



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>7</sup> : C07C 327/34, 69/618, 69/65, C07D 207/16, C07C 211/49, 219/10, C07D 209/28, 233/64, 277/06, 277/14, 295/088, 309/30, 401/12, 407/04, 417/12, 473/08, 495/04, 499/32, C07F 9/38, C07H 15/252, A61K 31/16</p>	A2	<p>(11) International Publication Number: <b>WO 00/61549</b></p> <p>(43) International Publication Date: 19 October 2000 (19.10.00)</p>
<p>(21) International Application Number: PCT/EP00/03237</p> <p>(22) International Filing Date: 11 April 2000 (11.04.00)</p> <p>(30) Priority Data: MI99A000750 13 April 1999 (13.04.99) IT</p> <p>(71) Applicant (<i>for all designated States except US</i>): NICOX S.A. [FR/FR]; 45, Avenue Kléber, F-75116 Paris (FR).</p> <p>(72) Inventor; and (75) Inventor/Applicant (<i>for US only</i>): DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT).</p> <p>(74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni 2, I-20129 Milano (IT).</p>		<p>(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i></p>
<p>(54) Title: PHARMACEUTICAL COMPOUNDS</p> <p>(57) Abstract</p> <p>Compounds or their salts of general formula (I): A-(B) wherein A = R-T<sub>1</sub>-, wherein R is the drug radical and T<sub>1</sub> = (CO)<sub>t</sub> or (X)<sub>t'</sub>, wherein X = O, S, NR<sub>1C</sub>, R<sub>1C</sub> is H or an alkyl having from 1 to 5 carbon atoms, or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1; B = -T<sub>B</sub>-X<sub>2</sub> wherein T<sub>B</sub> = (CO) when t = 0, T<sub>B</sub> = X when t' = -, X being as above defined; X<sub>2</sub>, monovalent radical, is such that the precursor drug of A and the precursor of B respectively meet the pharmacological tests described in the application.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Larvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

"PHARMACEUTICAL COMPOUNDS"

\* \* \* \* \*

The present invention relates to novel drugs for systemic use and non systemic use, and the compositions thereof, to be used in oxidative stress and/or endothelial dysfunctions cases.

By oxidative stress it is meant the generation of free radicals or radicalic compounds, which causes injury both of the cell and that of the surrounding tissue (Pathophysiology: the biological basis for disease in adults and children, McCance & Huether 1998 pages 48-54).

By endothelial dysfunctions it is meant those relating to the vasal endothelium. The damage of the vasal endothelium is known as one of those important events that can cause a series of pathological processes affecting various organs and body apparatuses, as described hereinafter (Pathophysiology: The biological basis for disease in adults and children, McCance & Huether 1998 page 1025).

As known, the oxidative stress and/or the endothelial dysfunctions are associated to various pathologies as reported hereinafter. The oxidative stress can also be caused by toxicity of a great variety of drugs, which significantly affects their performances.

Said pathological events are of a chronic, debilitating character and are very often typical of the elderly. As already said, in said pathological conditions the drugs used show a remarkably worsened performance.

Examples of pathological situations caused by the oxidative stress and/or by the endothelial dysfunctions, or present in elderly, are the following:

- For the cardiovascular system: myocardial and vascular ischaemia in general, hypertension, stroke, arteriosclerosis, etc.
- For the connective tissue: rheumatoid arthritis and connected inflammatory diseases, etc.
- For the pulmonary system: asthma and connected inflammatory diseases, etc.
- For the gastrointestinal system: ulcerative and non ulcerative dyspepsias, intestinal inflammatory diseases, etc.
- For the central nervous system: Alzheimer disease, etc.
- For the urogenital system: impotence, incontinence.
- For the cutaneous system: eczema, neurodermatitis, acne.
- The infective diseases in general (ref.: Schwarz-KB, Brady "Oxidative stress during viral infection: A review" Free radical Biol. Med. 21/5, 641-649 1996).

Further the ageing process can be considered as a true pathologic condition (ref. Pathophysiology: the biological



basis for disease in adults and children, pages 71-77).

The known drugs when administered to patients having pathologies associated to oxidative stress and/or endothelial dysfunctions, show a lower activity and/or higher toxicity.

This happens for example for drugs such as the antiinflammatory, cardiovascular drugs, respiratory apparatus drugs, central nervous system drugs, bone system drugs, antibiotics, urogenital, endocrine drugs, etc.

Drug research is directed to find new molecules having an improved therapeutic index (efficacy/toxicity ratio) or a lower risk/benefit ratio, also for pathological conditions as those above mentioned, wherein the therapeutic index of a great number of drugs results lowered. In fact in the above mentioned conditions of oxidative stress and/or endothelial dysfunctions, many drugs show a lower activity and/or higher toxicity.

For instance antiinflammatory drugs, such as NSAIDs and anticolitic drugs, such as 5-aminosalicylic acid and its derivatives, show the following drawbacks herein mentioned. NSAIDs result toxic particularly when the organism is debilitated or affected by morbid conditions associated to oxidative stress. Said conditions are for example the following: age, pre-existing ulcer, pre-existing gastric bleeding, debilitating chronic diseases such as in particular those affecting cardiovascular, renal apparatuses, the haematic crisis, etc. ("Misoprostol reduces serious gastrointestinal

complications in patients with rheumatoid arthritis receiving non-steroidal anti-inflammatory drugs. A randomized, double blind, placebo-controlled trial." F.E. Silverstein et Al., Ann. Intern. Med. 123/4, 241-9, 1995; Martindale 31a ed. 1996, pag. 73, Current Medical Diagnosis and Treatment 1998, pages 431 and 794).

The administration of anti-inflammatory drugs to patients in the above mentioned pathological conditions can be made only at doses lower than those used in therapy in order to avoid remarkable toxicity phenomena. Thus anti-inflammatory activity results poor.

Beta-blockers, used for the angina, hypertension and cardiac arrhythmia treatment, show side effects towards the respiratory apparatus (dyspnoea, bronchoconstriction), and therefore they can cause problems in patients affected by pathologies to said organs (asthma, bronchitis). Therefore beta-blockers can even worsen respiratory diseases such as asthma. Therefore in asthmatic patients reduced doses of said drugs must be used in order not to jeopardize even more the respiratory functionality. Thus the efficacy of the beta-blockers results very reduced.

Antithrombotics, such as for example dipyridamole, aspirin, etc., used for the prophylaxis of thrombotic phenomena, have the same drawbacks. In patients affected by pathologies connected to oxidative stress and/or endothelial

dysfunctions, the therapeutic action or the tolerability of these drugs, as in the case of aspirin, is greatly reduced.

Bronchodilators for example salbutamol, etc., are used in the asthma and bronchitis treatment and drugs active on the cholinergic system are used in pathologies such as urinary incontinence. Their administration can produce similar side effects affecting the cardiovascular apparatus, causing problems both to cardiopathic and to hypertensive patients. Cardiopathies and hypertension are pathologies associated, as above said, to the oxidative stress and/or endothelial dysfunctions. Also these drugs show the same drawbacks as those above mentioned.

Expectorant and mucolytic drugs, which are used in the therapy of inflammatory states of the respiratory organs, show drawbacks in patients affected by the above described conditions. Their administration can give rise to heartburn and gastric irritability, particularly in the elderly.

Bone resorption inhibitors, such as diphosphonates (for example alendronate, etc.) are drugs showing high gastrointestinal toxicity. Therefore also these drugs can show the same drawbacks as those above mentioned.

Phosphodiesterase inhibitors, such as for example sildenafil, zaprinast, used in the cardiovascular and respiratory system diseases, are characterized by similar problems as to tolerability and/or efficacy in the mentioned

pathological conditions of oxidative stress and/or endothelial dysfunctions.

Antiallergic drugs, for example cetirizine, montelukast, etc. show similar problems in the mentioned pathological conditions, particularly for that it concerns their efficacy.

Anti-angiotensin drugs, f.i. ACE-inhibitors, for example enalapril, captopril, etc., and receptor inhibitors, for example losartan, etc., are used in the cardiovascular disease treatment. Their drawback is to give side effects to the respiratory apparatus (i.e. cough, etc.) in the above mentioned pathological conditions.

Antidiabetic drugs, both of the insulin-sensitizing and of hypoglycaemizing type, such as for example sulphonylureas, tolbutamide, glypiride, glyclazide, glyburide, nicotinamide etc., are ineffective in the prophylaxis of diabetic complications. Their administration can give rise to side effects, such as for example gastric lesions. These phenomena become more intense in the pathological conditions above mentioned.

Antibiotics, for example ampicillin, clarithromycin, etc., and antiviral drugs, acyclovir, etc., show problems as regards their tolerability, for example they cause gastro-intestinal irritability.

Antitumoral drugs, for example doxorubicin, daunorubicin, cisplatinum, etc., have high toxicity, towards different

organs, among which are stomach and intestine. Said toxicity is further worsened in the above mentioned pathologies of oxidative stress and/or endothelial dysfunctions.

Antidementia drugs for example nicotine and colinomimetics, are characterized by a poor tolerability especially in the above mentioned pathologies.

Drugs having a steroidal structure which are used in the therapy of acute (asthma, etc.) or chronic diseases (intestinal, hepatic, respiratory diseases, female reproductive apparatus diseases, cutaneous diseases, etc.) are characterized by marked toxic effects affecting various organs, particularly in the above mentioned oxidative stress conditions.

The class of steroidal drugs, among which hydrocortisone, cortisone, prednisone, prednisolone, fludrocortisone, desoxycorticosterone, methylprednisolone, triamcinolone, paramethasone, betamethasone, dexamethasone, triamcinolone acetonide, fluocinolone acetonide, beclomethasone, acetoxypregnelone, etc., has remarkable farmaco-toxicological effects on various organs, and for this reason both their clinical use and its interruption cause a series of side effects, some of which very serious. See for example Goodman & Gilman, "The pharmaceutical Basis of Therapeutics" 9<sup>ed.</sup>, pag. 1459-1465, 1996.

Among said toxic effects can be mentioned those affecting the bone tissue leading to an altered cellular metabolism and

an high osteoporosis incidence; those affecting the cardiovascular system, generating an hypertensive response; those affecting the gastrointestinal apparatus giving gastric damages.

See for example Martindale "The extrapharmacopoeia", 30th ed., pag. 712-723, 1993.

To the class of steroidal drugs belong also biliary acids, that have been used in the therapy of hepatic dysfunctions and in biliary colics. Ursodesoxycholic acid is also used in some hepatic dysfunctions (hepatic cirrhosis of biliary origin, etc.). Their tolerability is strongly worsened in the presence of gastrointestinal complications (chronic hepatic damage, peptic ulcer, intestinal inflammation, etc.). Also in the case of biliary acids the oxidative stress remarkably affects drug performance: both the efficacy and the tolerability of chenodeoxycholic and ursodesoxycholic acids are significantly reduced. In particular the unwanted effects on liver are found exalted. Among the steroidal compounds can be mentioned also estrogens for the treatment of dislipidaemias, hormonal dysfunctions, female apparatus tumours treatment can be mentioned. Also said steroids show side effects as above mentioned, in particular at the hepatic level.

According to the above mentioned prior art it seems almost impossible to separate therapeutic activity from side effects, see Goodman et al, above mentioned, at p. 1474.

The need was felt to have available drugs showing an improved therapeutic performance, i.e. endowed both of a lower toxicity and/or higher efficacy, so that they could be administered to patients in morbid conditions of oxidative stress and/or endothelial dysfunctions, without showing the drawbacks of the drugs of the prior art.

It has now surprisingly and unexpectedly found that the aforementioned problems evidenced the administration of drugs, to patients affected by oxidative stress and/or endothelial dysfunctions, or to the elderly in general, are solved by a new class of drugs as described hereinafter.

An object of the invention are compounds or their salts having the following general formula (I):



wherein:

$A = R-T_1-$ , wherein

R is the drug radical and

$T_1 = (CO)_t$  or  $(X)_{t'}$ , wherein  $X = O, S, NR_{1C}$ ,  $R_{1C}$  is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, or a free valence, t and t' are integers and equal to zero or 1, with the proviso that  $t = 1$  when  $t' = 0$ ;  $t = 0$  when  $t' = 1$ ;

$B = -T_B-X_2$  wherein

$T_B = (CO)$  when  $t = 0$ ,  $T_B = X$  when  $t' = 0$ , X being as above defined;

$X_2$ , monovalent radical, is such that the corresponding precursor of B meets test 5 and/or test 4; said precursor of formula  $-T_B-X_2$ , wherein the  $T_B$  free valence is saturated with  $-OZ$  or  $Z$  wherein  $Z = H$  or  $R_{1a}$ ,  $R_{1a}$   $C_1-C_{10}$  being = linear or when possible branched alkyl, preferably  $C_1-C_5$ ,

or with  $-Z^I-N-Z^{II}$ ,  $Z^I$  and  $Z^{II}$  being equal or

different and have the  $Z$  values, depending on whether  $T_B = CO$  or  $X$ , in connection with the  $t$ ,  $t'$  values;

with the proviso that:

the drug  $A = R-T_1-$ , wherein the free valence is saturated as hereinafter mentioned:

- when  $t' = 0$  with:
  - $O-Z$  wherein  $Z = H$  or  $R_{1a}$  as above defined, or with
  - $Z^I-N-Z^{II}$ ,  
 $\quad \quad \quad |$   
 $Z^I$  and  $Z^{II}$  being as above defined,
- when  $t = 0$  with  $X-Z$ , wherein  $X$  and  $Z$  as above defined,

is such as to meet at least one of following tests 1-3;

wherein test 1 (NEM) is a test in vivo carried out on four groups of rats (each formed by 10 rats), the controls (two groups) and the treated (two groups) of which one group of the controls and one group of the treated respectively are administered with one dose of 25 mg/kg s.c. of N-ethylmaleimide



(NEM), the controls being treated with the carrier and the treated groups with the carrier + the drug of formula  $A = R-T_1$  - wherein the free valence is saturated as above indicated, administering the drug at a dose equivalent to the maximum one tolerated by the rats that did not receive NEM, i.e. the highest dose administrable to the animal at which there is no manifest toxicity, i.e. such as to be symptomatologically observable; the drug complies with test 1, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in the group treated with NEM + carrier + drug are observed gastrointestinal damages greater than those of the group treated with the carrier, or of the group treated with the carrier + drug, or of the group treated with the carrier + NEM;

wherein test 2 (CIP) is a test in vitro wherein human endothelial cells from the umbilical vein are harvested under standard conditions, then divided into two groups (each group replicated five times), of which one is treated with a mixture of the drug  $10^{-4}$  M concentration in the culture medium, the other group with the carrier; then cumene hydroperoxide (CIP) having a 5 mM concentration in the culture medium is added to each of the two groups; the drug meets test 2, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), if a statistically significant inhibition of the

apoptosis (cellular damage) induced by CIP is not obtained with  $p < 0.01$  with respect to the group treated with the carrier and CIP;

wherein test 3 (L-NAME) is a test in vivo carried out on four groups of rats (each group formed by 10 rats) for 4 weeks and receiving drinking water, the controls (two groups) and the treated (two groups), of which one group of the controls and of the treated respectively receives in the above 4 weeks drinking water added of N- $\omega$ -nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/litre, the controls in the 4 weeks being administered with the carrier and the treated in the 4 weeks with the carrier + the drug, administering the carrier or the drug + carrier once a day, the drug being administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME, i.e., the highest dose administrable to animals at which no manifest toxicity appears, i.e. such as to be symptomatologically observable; after the said 4 weeks, the water supply is stopped for 24 hours and then sacrificed, determining the blood pressure 1 hour before sacrifice, and after sacrifice of the rats determining the plasma glutamic pyruvic transaminase (GPT) after sacrifice, and examining the gastric tissue; the drug meets test 3, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when in the group of rats treated with L-NAME + carrier + drug, greater hepatic damages (determined as higher values of GPT)

and/or gastric and/or cardiovascular damages (determined as higher values of blood-pressure) are found in comparison in comparison respectively with the group treated with the carrier alone, or with the group treated with the carrier + drug, or with the group treated with the carrier + L-NAME;

wherein test 4 is an analytical determination carried out by adding portions of methanol solutions of the precursor of B at a  $10^{-4}$  M concentration, to a methanol solution of DPPH (2,2-diphenyl-1-picryl hydrazyl - free radical); after having maintained the solution at room temperature away from light for 30 minutes, it is read the absorbance at the wave length of 517 nm of the test solution and of a solution containing only DPPH in the same amount as in the test solution; and then the inhibition induced by the precursor towards the radical production by DPPH is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein  $A_s$  and  $A_c$  are respectively the absorbance values of the solution containing the test compound + DPPH and that of the solution containing only DPPH; the acceptance criterium of the compounds according to this test is the following: test 4 is met by B precursor compounds if the inhibition percentage as above defined is higher than or equal to 50%;

wherein test 5 is the following: it is an analytical determination carried out by adding aliquots of  $10^{-4}$  M

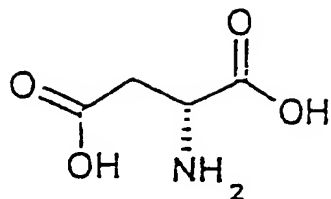
methanol solutions of the precursor of B having the free valence saturated as above indicated, to a solution formed by admixing a 2 mM solution of desoxyribose in water with 100 mM of phosphate buffer and 1 mM of the salt  $\text{Fe}^{\text{II}}(\text{NH}_4)_2(\text{SO}_4)_2$ ; after having thermostatted the solution at 37°C for one hour, are added, in the order, aliquots of aqueous solutions of trichloroacetic acid 2.8% and of thiobarbituric acid 0.5 M, heating is effected at 100°C for 15 minutes and the absorbance of the tested solutions is then read at 532 nm; the inhibition induced by the precursor of B or B<sub>1</sub> or C = -T<sub>C</sub>-Y-H in the confront of radical production by  $\text{Fe}^{\text{II}}$  is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

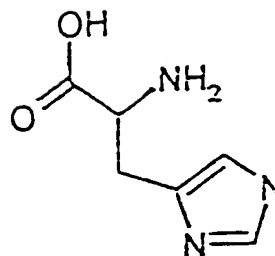
wherein A<sub>s</sub> and A<sub>c</sub> are respectively the absorbance values of the solution containing the tested compound and the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage as above defined of the precursor of B is higher than or equal to 50%.

Preferably the compound precursor of B which meets test 5 is selected from the following compounds:

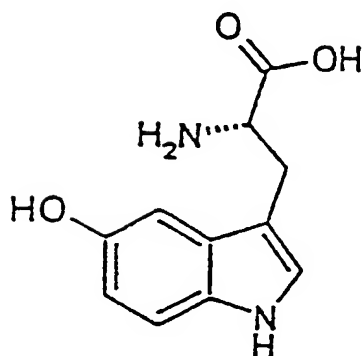
- Aminoacids: aspartic acid (PI), histidine (PII), -  
5-hydroxytryptophan (PIII), 4-thiazolidincarboxylic acid  
(PIV), 2-oxo-4-thiazolidincarboxylic acid (PV)



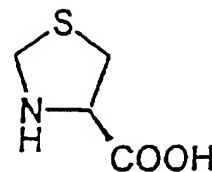
(PI)



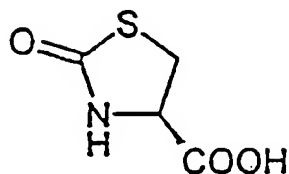
(PII)



(PIII)



(PIV)

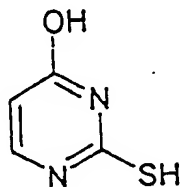


(PV)

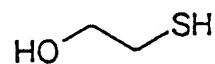
mono and polyalcohols or thiols:

2-thiouracil (QI), 2-mercaptoethanol (QII), esperidine (QIII), secalciferol (QIV), 1- $\alpha$ -OH vitamin D2 (QV), flocalcitriol (QVI), 22-oxacalcitriol (QVII), the vitamin D3 derivative esterified with the vitamin A radical (QVIII), the compound of formula (QIX), 24,28-methylene-

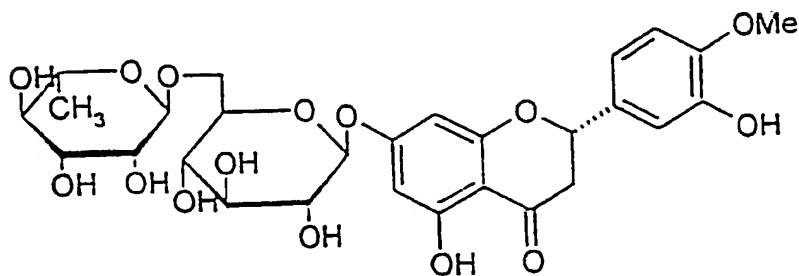
1 $\alpha$ -hydroxyvitamin D<sub>2</sub> (QX) the compound derived from 1 $\alpha$ ,25-dihydroxyvitamin D<sub>2</sub> (QXI), 2-mercaptoimidazol (QXII)



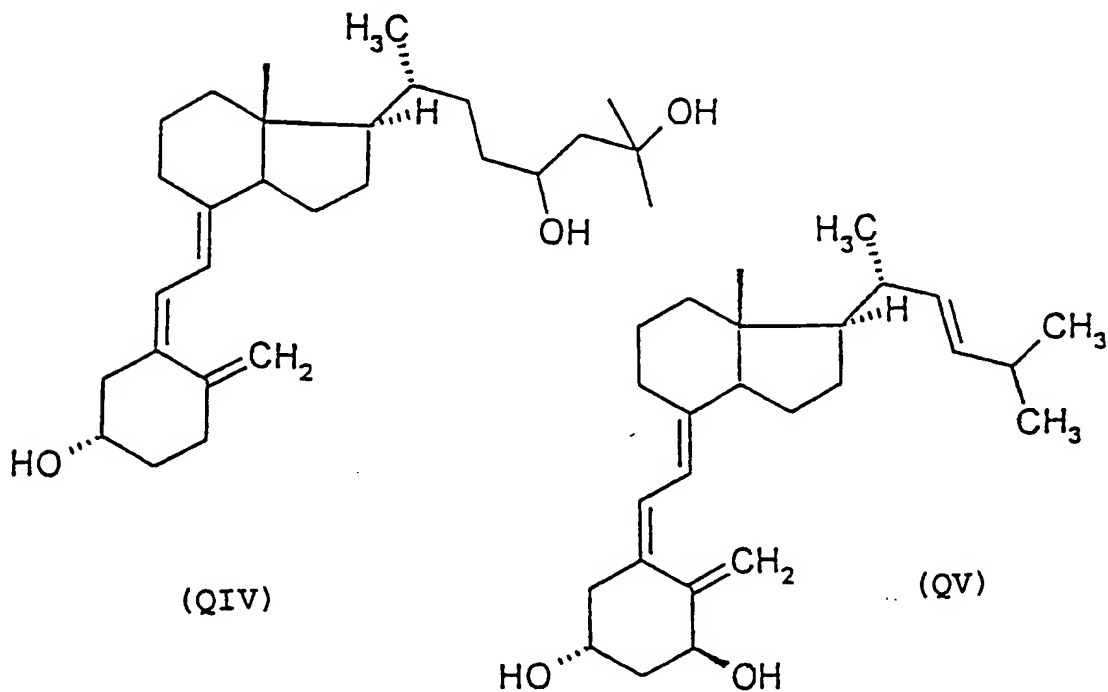
(QI)



(QII)



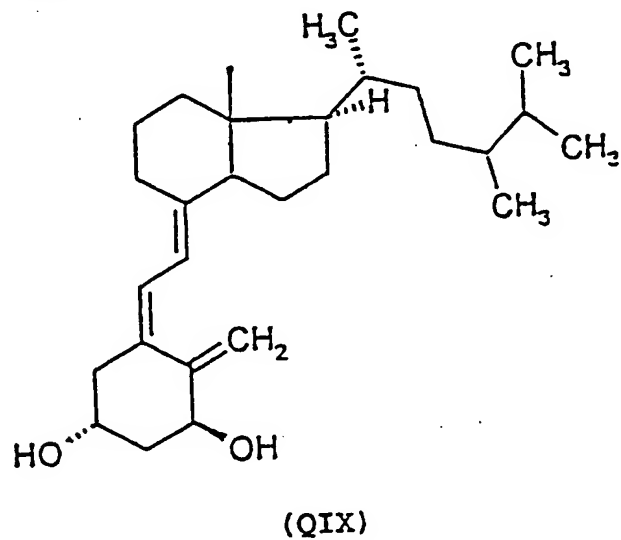
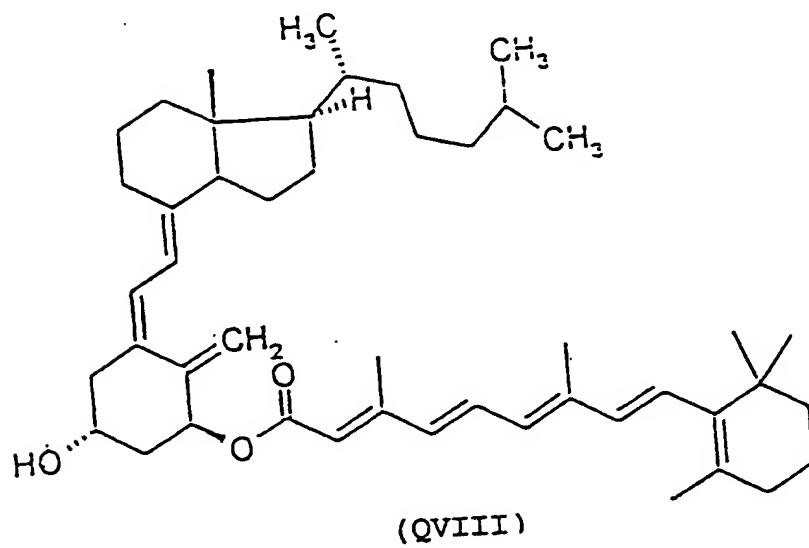
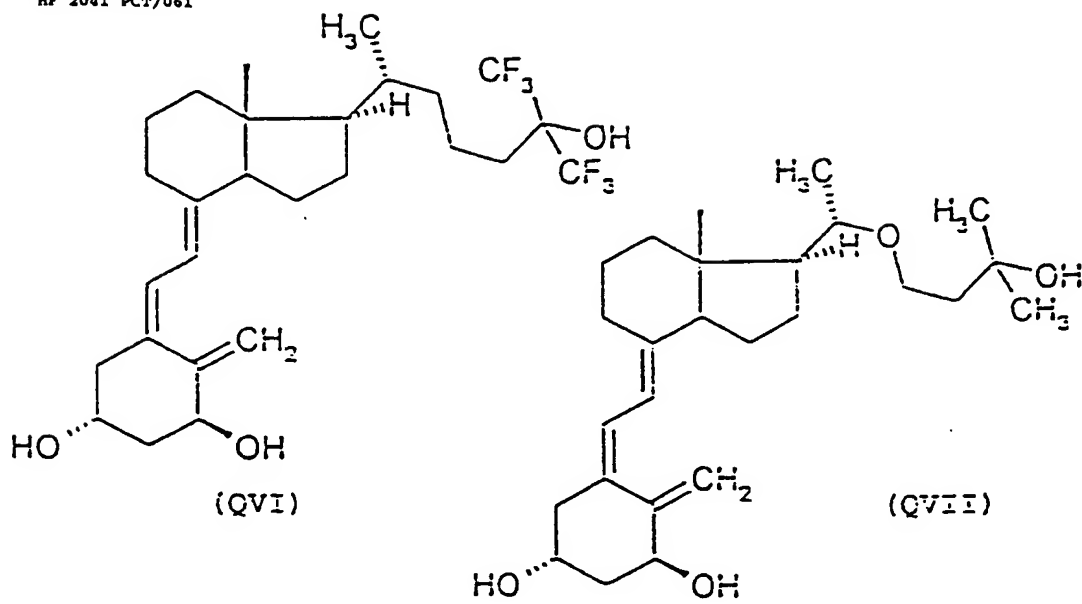
(QIII)

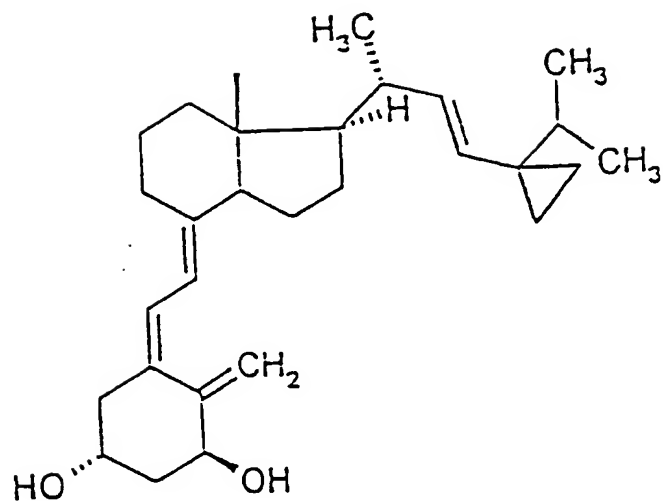


(QIV)

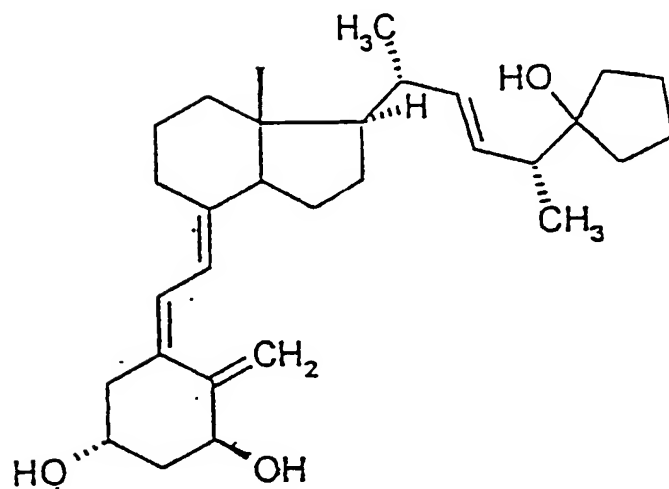
(QV)

HF 2041 PCT/061

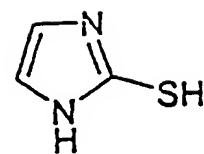




(QX)

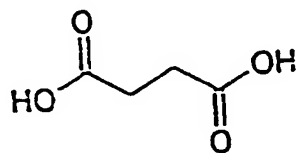


(QXI)

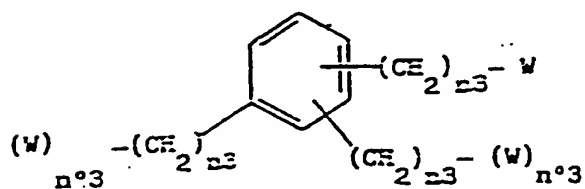


(QXII)

- succinic acid (RI)



(RI)



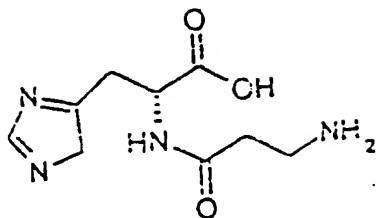
(RII)



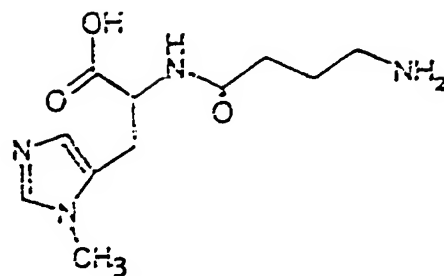
wherein  $n^{\circ}3$ , equal to or different from each other, are an integer equal to zero or one;  $n3$ , equal to or different from each other, are integers from zero to three;  $W$ , equal to or different from each other, are selected among the following:  $HX$  with  $X$  as above defined,  $COOH$ ,  $R'$ ,  $OR'$  wherein  $R'$  is a linear or branched when possible alkyl having from 1 to 20 carbon atoms, preferably from 1 to 6 carbon atoms;  $R_f$ ,  $OR_f$  wherein  $R_f$  is as  $R'$  but containing at least one halogen atom instead of  $H$ , preferably  $F$ ; at least one of the  $W$  radicals is  $XH$ , when the drug reactive function is a carboxyl; or  $COOH$  when the drug reactive function is  $XH$ ; when  $n^{\circ}3 = 0$  if  $n3$  is different from zero then the free valence of the  $n3$  group is saturated with one of the following substituents:  $R'$ ,  $OR'$ ,  $R_f$ ,  $OR_f$ ,  $H$ ; when  $n^{\circ}3 = 0$  and  $n3 = 0$ , the free valence is saturated with  $H$ .

Preferably the precursor compound of  $B$  which meets test 4 is selected from the following classes of compounds:

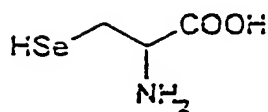
- Aminoacids, selected from the following: L-carnosine (formula CI), anserine (CII), selenocysteine (CIII), selenomethionine (CIV), penicillamine (CV), N-acetylpenicillamine (CVI), cysteine (CVII), N-acetylcysteine (CVIII), glutathione (CIX) or its esters, preferably ethyl or isopropyl ester:



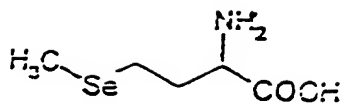
(CI)



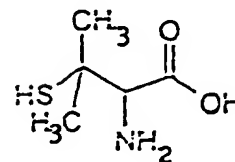
(CII)



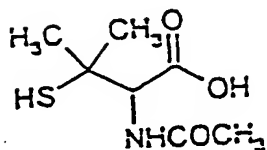
(CIII)



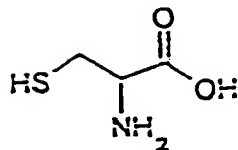
(CIV)



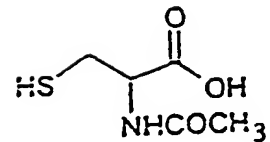
(CV)



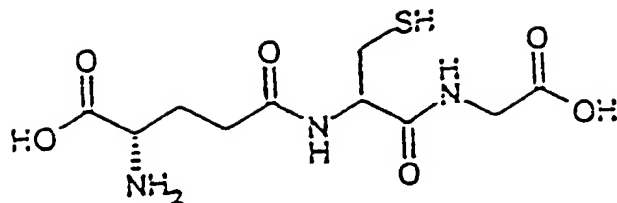
(CVI)



(CVII)



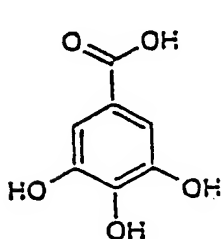
(CVIII)



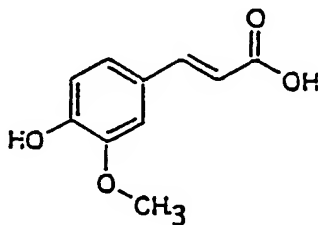
(CIX)

For the compounds (CV), (CVI), (CVII) and (CVIII) wherein a SH group is present, the corresponding compound  $SN(O)_s$ , wherein s is 1 or 2, can also be used instead of SH;

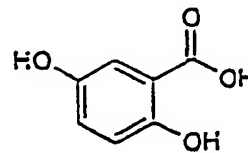
- hydroxyacids, selected from the following: gallic acid (formula DI), ferulic acid (DII), gentisic acid (DIII), citric acid (DIV), caffeic acid (DV), hydrocaffeic acid (DVI), p-coumaric acid (DVII), vanillic acid (DVIII), chlorogenic acid (DIX), kynurenic acid (DX), syringic acid (DXI):



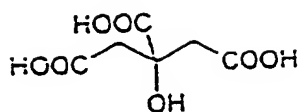
(DI)



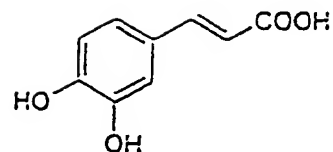
(DII)



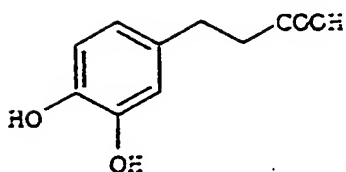
(DIII)



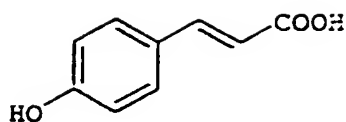
(DIV)



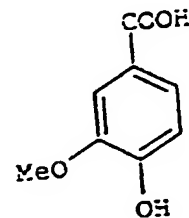
(DV)



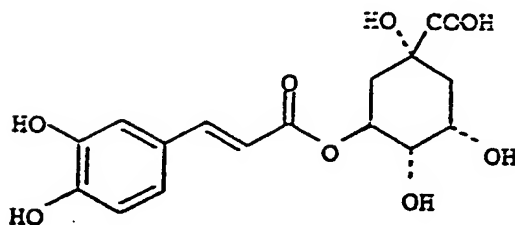
(DVI)



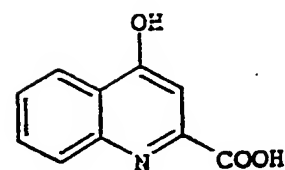
(DVII)



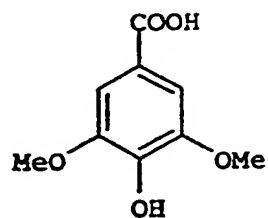
(DVIII)



(DIX)



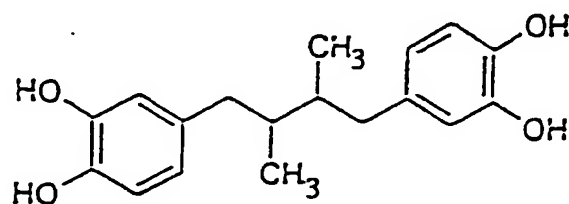
(DX)



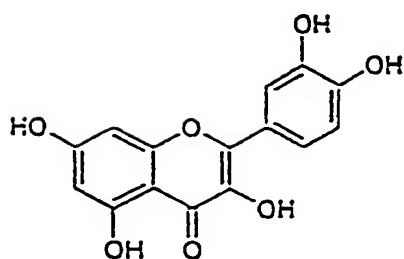
(DXI)

- Aromatic and heterocyclic mono- and polyalcohols, selected from the following: nordihydroguaiaretic acid (EI), quercetin (EII), catechin (EIII), kaempferol (EIV),

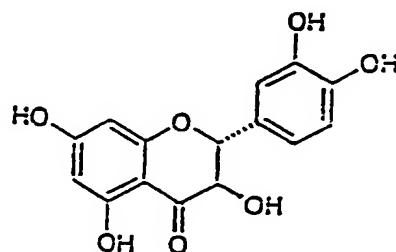
sulphurethyne (EV), ascorbic acid (EVI), isoascorbic acid (EVII), hydroquinone (EVIII), gossypol (EIX), reductic acid (EX), methoxyhydroquinone (EXI), hydroxyhydroquinone (EXII), propyl gallate (EXIII), saccharose (EXIV), vitamin E (EXV), vitamin A (EXVI), 8-quinolol (EXVII), 3-tert-butyl-4-hydroxyanisole (EXVIII), 3-hydroxyflavone (EXIX), 3,5-tert-butyl-p-hydroxytoluene (EXX), p-tert-butyl phenol (EXXI), timolol (EXXII), xibornol (EXXIII), 3,5-di-ter-butyl-4-hydroxybenzyl-thioglycolate (EXXIV), 4'-hydroxybutyranilide (EXXV), guaiacol (EXXVI), tocol (EXXVII), isoeugenol (EXXVIII), eugenol (EXXIX), piperonyl alcohol (EXXX), allopurinol (EXXXI), conyferyl alcohol (EXXXII), 4-hydroxyphenetyl alcohol (EXXXIII), p-coumaric alcohol (EXXXIV), curcumin (EXXXV):



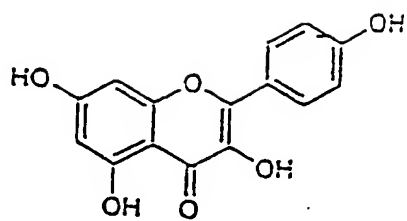
(EI)



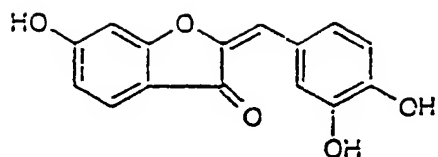
(EII)



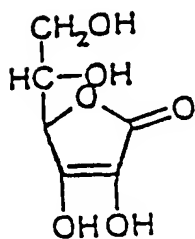
(EIII)



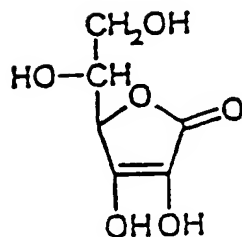
(EIV)



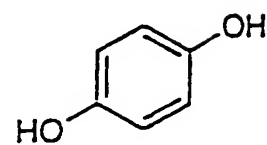
(EV)



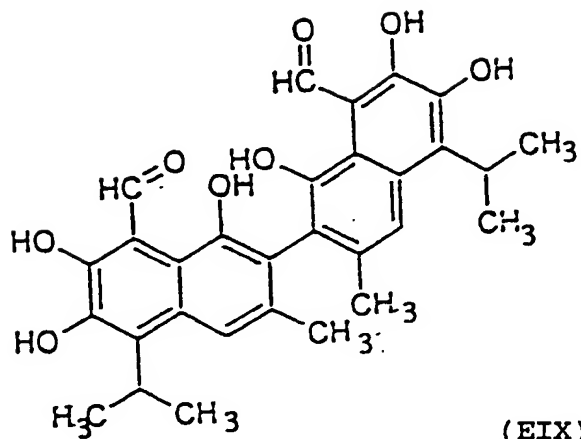
(EVI)



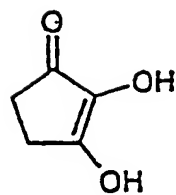
(EVII)



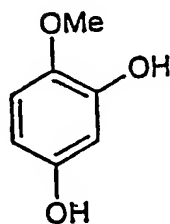
(EVIII)



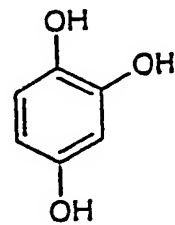
(EIX)



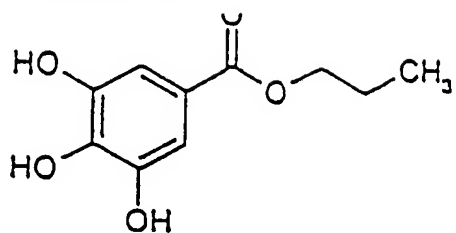
(EX)



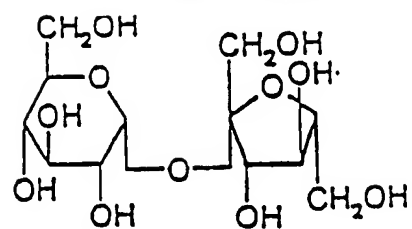
(EXI)



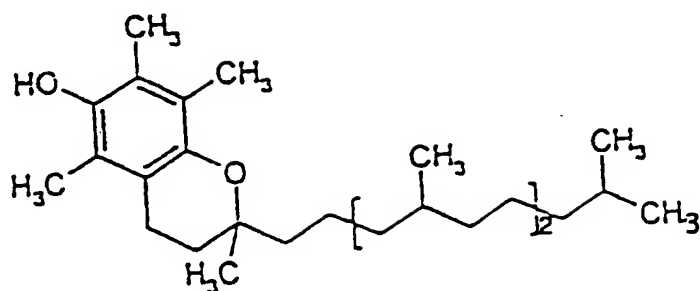
(EXII)



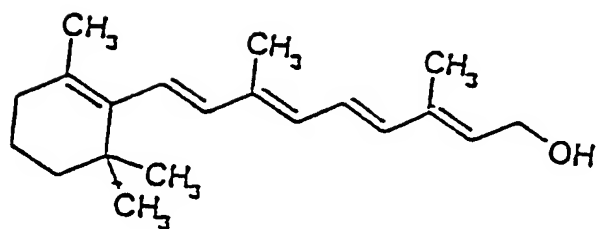
( EXIII )



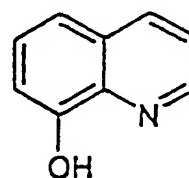
(EXIV)



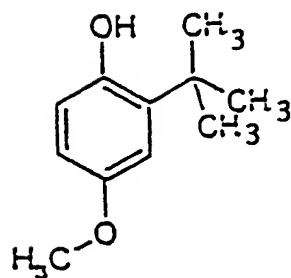
( EXV )



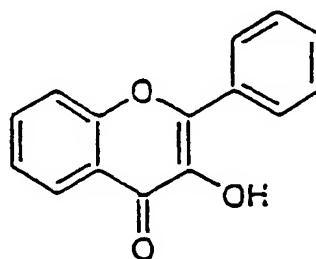
( EXVI )



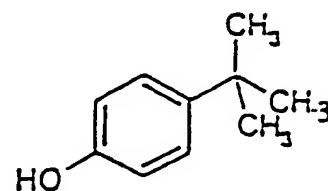
( EXVII )



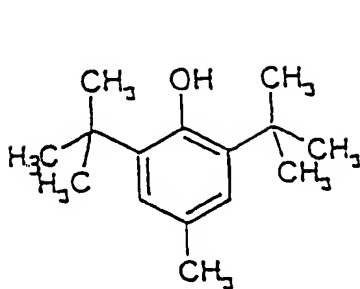
(EXVIII)



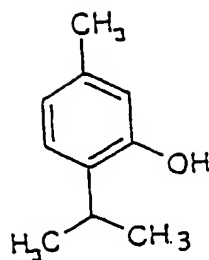
(EXIX)



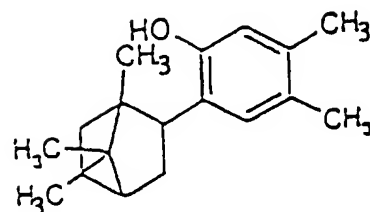
( EXXI )



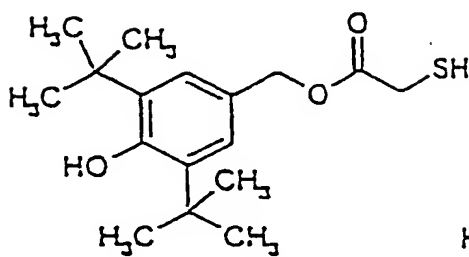
(EXX)



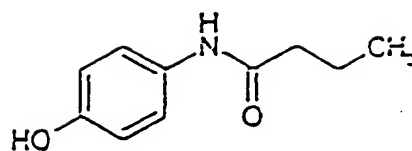
(EXXII)



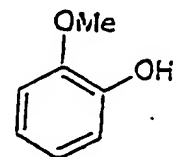
(EXXIII)



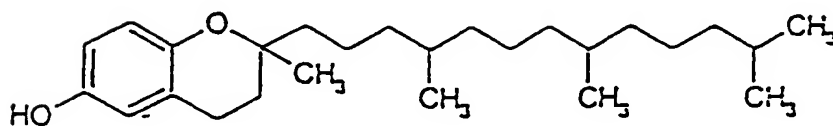
(EXXIV)



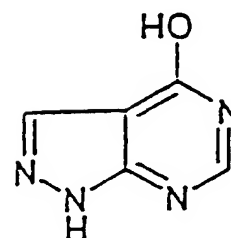
(EXXV)



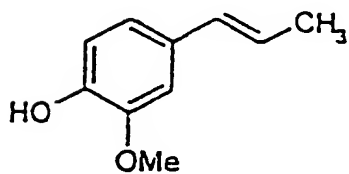
(EXXVI)



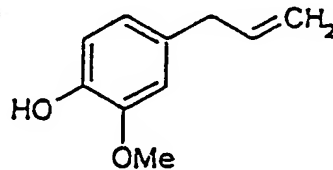
(EXXVII)



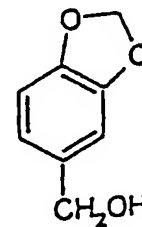
(EXXXI)



(EXXVIII)

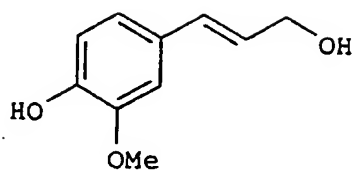


(EXXIX)

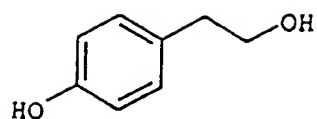


(EXXX)

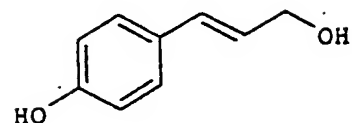




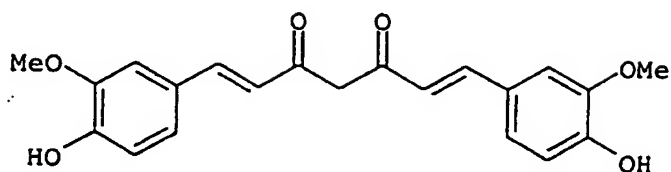
(EXXXII)



(EXXXIII)

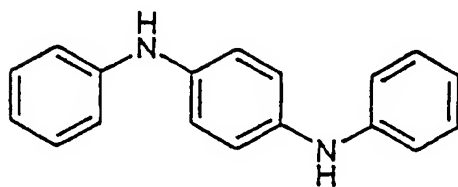


(EXXXIV)

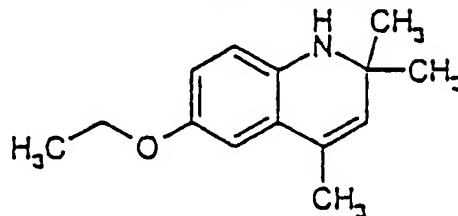


(EXXXV)

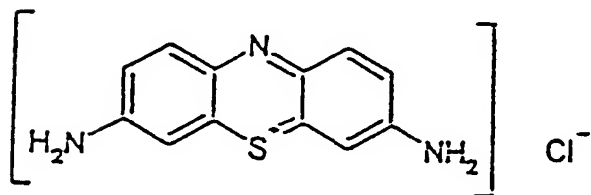
- aromatic and heterocyclic amines, selected from the following: N, N'-diphenyl-p-phenylenediamine (MI), ethoxyquin (MII), thionine (MIII), hydroxyurea (MIV):



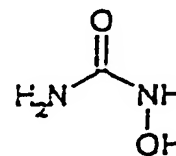
(MI)



(MII)

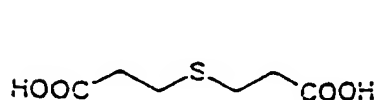


(MIII)

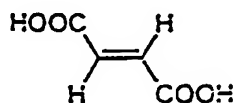


(MIV)

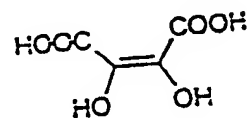
- Compounds containing at least a free acid function, selected from the following: 3,3'-thiodipropionic acid (NI), fumaric acid (NII), dihydroxymaleic acid (NIII), thioctic acid (NIV), edetic acid (NV), bilirubin (NVI), 3,4-methylenedioxycinnamic acid (NVII), piperonylic acid (NVIII):



(NI)



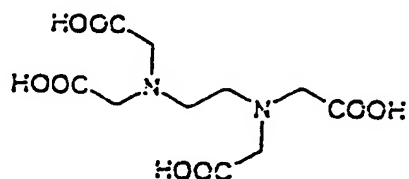
(NII)



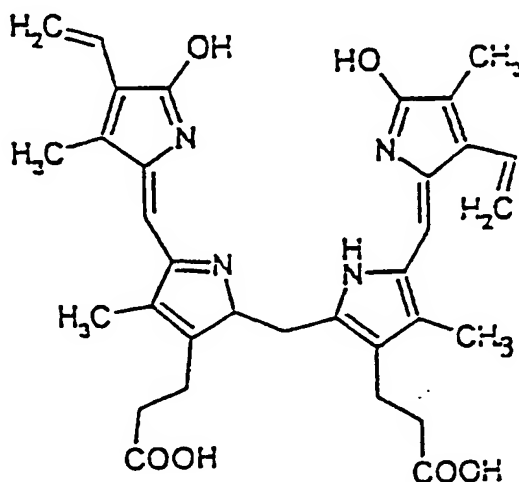
(NIII)



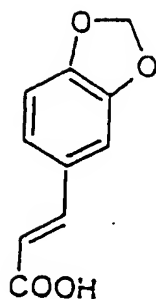
(NIV)



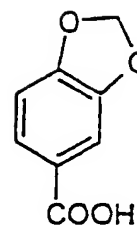
(NV)



(NVI)



(NVII)



(NVIII)

The drug and B precursor compounds are prepared according to the known methods in the prior art and described, for example, in "The Merck Index, 12a Ed. (1996), herein incorporated by reference.

The vitamin D3 derivative with retinoic acid (QVIII) is prepared as described in JP 93039261 (ref. C.A. 119 117617); the formula (QIX) compound according to EP 562497; 24,28-methylene-1 $\alpha$ -hydroxyvitamin D2 (QX) according to EP 578494; the derivative compound of dehydroxyvitamin D2 (QXI) according to EP 549318.

The preferred B compounds are those meeting test 4.

The tests carried out to identify the drug precursor of R radical of the formula (I) are in detail the following:

Test 1 (NEM): evaluation of the gastrointestinal damage from oxidative stress induced by free radicals formed following administration of N-ethylmaleimide (NEM) (H.G. Utley, F. Bernheim, P. Hochstein "Effects of sulphhydryl reagents on peroxidation in microsomes" Archiv. Biochem. Biophys. 118, 29-32

1967).

The animals (rats) are distributed in the following groups (no. 10 animals for group):

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, or a physiologic solution when parenterally administered, i.e. by subcutaneous, intraperitoneal, intravenous or intermuscular route),

2° group: treatment: carrier as above defined + NEM,

B) Groups treated with the drug:

group I: treatment: carrier + drug,

gruppo II: treatment: carrier + drug + NEM.

The administration routes are those known for the drug, and can be the oral or subcutaneous, intraperitoneal, intravenous or intramuscular route.

The NEM dose is of 25 mg/kg in physiologic solution (subcutaneous route) and the drug is administered one hour later, in suspension in the carrier, as a single dose which corresponds to the maximum one, or the highest still tolerated by the animals of the group of rats not pretreated with NEM, i.e. the highest administrable dose to said group at which there is no manifest toxicity in the animals, defined as a toxicity that is clearly recognizable for its symptoms. The animals are sacrificed after 24 hours and then one proceeds to

the evaluation of the damage to the gastrointestinal mucosa.

The drug meets test 1, i.e. it can be used to prepare the compounds of general formula (I) and (II), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in said group the gastrointestinal damages noticed are greater than those shown by the group treated with the carrier alone, or the group treated with carrier + drug, or the group treated with carrier + NEM, even though the drug pharmacotherapeutic efficacy, assayed by using specific tests, is not significantly reduced.

Test 2 (CIP): Protection parameter of endothelial cell against the oxidative stress induced by cumene hydroperoxide (CIP).

Human endothelial cells of the umbilical vein are prepared according to an usual standard procedure. Fresh umbilical veins are filled with a 0.1% by weight collagenase solution and incubated at 37°C for 5 minutes.

Afterwards the veins are perfused with medium M 199 (GIBCO, Grand Island, NY) pH 7.4 further added of other substances, as described in the examples. The cells are collected from the perfusate by centrifugation and harvested in culture flasks T-75, pretreated with human fibronectin. The cells are then harvested in the same medium, further added with 10 ng/ml of bovine hypothalamic growth factor. When the cells of the primary cell culture (i.e. that directly obtained from ex-vivo)

form a single layer of confluent cells (about 8,000,000 cells/flask), the culture is stopped and the layers washed and trypsinized. The cellular suspensions are transferred into the wells of a cell culture plate having 24 wells, half of which is then additioned with the same culture medium containing the drug at a  $10^{-4}$ M concentration, and harvested in a thermostat at 37°C at a constant moisture. Only the cells coming from said first sub-cultures are used for the experiments with cumene hydroperoxide (CIP). The cells are identified as endothelial cells by morphological examination and by their specific immunological reaction towards factor VIII; said cultures did not show any contaminations from myocytes or fibroblasts.

Before starting the test, the cellular culture medium is removed and the cellular layers are carefully washed with a physiologic solution at a temperature of 37°C. The wells of the culture plate are then incubated for one hour with CIP at a 5 mM concentration in the culture medium. The evaluation of cellular damage (apoptosis) is carried out by determining the per cent variation of the DNA fragmentation with respect to the control group (treated with CIP alone), evaluating the fluorescence variation at the wave length of 405-450 nm. 5 replicates for each sample are carried out.

The drug meets the test, i.e. it can be used for preparing the compounds of general formula (I) and (II), when a statistically significant inhibition of apoptosis (cellular damage)

induced by CIP with respect to the group treated with CIP alone is not obtained at  $p < 0.01$ .

Test 3 (L-NAME): evaluation of the endothelial dysfunction induced by administration of L-NAME ( $N^w$ -nitro-L-arginine-methyl ester) J. Clin. Investigation 90, 278-281, 1992.

The endothelial dysfunction is evaluated by determining the damage to the gastrointestinal mucosa, the hepatic damage and blood hypertension induced by administration of L-NAME.

The animals (rats) are divided in groups as herein below shown. The group receiving L-NAME is treated for 4 weeks with said compound dissolved at a concentration of 400 mg/litre in drinking water. The following groups are constituted (No. 10 animals for group):

A) Control groups:

1° group: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when administered parenterally),

2° group: carrier + L-NAME,

B) Groups administered with the drug:

3° group: carrier + drug,

4° group: carrier + drug + L-NAME.

The administration routes are those known for the drug, and can be the oral or subcutaneous, intraperitoneal, intravenous or intramuscular route. The drug is administered at

that dose which results the highest still tolerated by the animals of the group of rats not pretreated with L-NAME, i.e. the highest administrable dose at which there is no evident toxicity in the animals, i.e a toxicity recognizable for its symptoms. The drug is administered once a day for 4 weeks.

At the end of the four weeks treatment access to water is prevented and after 24 hours the animals are sacrificed.

One hour before the sacrifice blood-pressure is determined, and a blood pressure increase is taken as an evaluation of the damage to vascular endothelium. The damage to the gastric mucosa is evaluated as illustrated in test 1 (see example F1). The hepatic damage is determined by evaluation of the glutamic-pyruvic transaminase (GPT increase) after sacrifice.

The drug meets test 3, i.e. it can be used for preparing the compounds of general formula (I) and (II), when in the group of rats treated with L-NAME + drug + carrier it is found an higher hepatic damage (GPT) and/or an higher gastric damage and/or an higher cardiovascular (blood-pressure) damage in comparison to that of the group treated with the carrier alone, or of the group treated with carrier + drug, or of the group treated with carrier + L-NAME; even if the drug pharmacotherapeutic efficacy, assayed by specific tests, is not significantly reduced.

Under the conditions indicated in the above described in



vivo tests 1 and 3 the therapeutic index of the drug is reduced since the usual doses at which the drug can be effective are no longer tolerated.

Test 4 is a colorimetric test which affords to establish whether the precursor of B inhibits the production of radicals from DPPH (2,2-diphenyl-1-picryl-hydrazyl) (M.S. Nenseter et Al., Atheroscler. Thromb. 15, 1338-1344, 1995). 100  $\mu$ M solutions in methanol of the tested substances are prepared, and an aliquot of each of said solutions is added to a DPPH solution in methanol 0.1 M. After having stored the solutions at room temperature away from light for 30 minutes, their absorbances are read at the wave length of 517 nm, together with that of the corresponding DPPH solution at the same concentration. The absorbance decrease with respect to that of the solution of DPPH at the same concentration of the test solutions is determined. The effectiveness of the tested compound in inhibiting formation of radicals by DPPH is expressed by the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein  $A_s$  and  $A_c$  are respectively the absorbance values of the solution containing the test compound together with DPPH and of the solution containing only DPPH.

The compound precursor of B meets test 4 when the inhibition percentage of radical production from DPPH, expressed as a percentage according to the above equation, is

higher than or equal to 50%.

Test 5 is a colorimetric test wherein 0.1 ml aliquots of  $10^{-4}$  M methanolic solutions of the tested products are added to test tubes containing a solution formed by 0.2 ml of 2 mM deoxyribose, 0.4 ml of phosphate buffer pH 7.4 100 mM and 0.1 ml of 1 mM  $\text{Fe}^{\text{II}}(\text{NH}_4)_2(\text{SO}_4)_2$  in 2mM HCl. The test tubes are then maintained at 37°C for one hour. Then in each test tube are added, in the order, 0.5 ml of a 2.8% solution in tri-chloroacetic acid water and 0.5 ml of an aqueous 0.1 M solution of thiobarbituric acid. A reference blank is formed by adding to a test tube containing only the above described aqueous solution of reactants 0.1 ml of methanol. The test tubes are closed and heated in an oil bath at 100°C for 15 minutes. A pink coloration is developed the intensity of which is proportional to the quantity of deoxyribose undergone to radical oxidative degradation. The solutions are cooled at room temperature and their absorbances are read at 532 nm against the blank. The inhibition induced by the precursor of B in the confront of radical production by  $\text{Fe}^{\text{II}}$  is determined by means of the following formula:

$$(1 - A_g/A_c) \times 100$$

wherein  $A_g$  and  $A_c$  are respectively the absorbance values of the solution containing the tested compound + the iron salt and that of the solution containing only the iron salt, the compound satisfies test 5 when the inhibition percentage of

radical production as above defined from the precursor of B is higher than or equal to 50%.

Unexpectedly the products of the invention of formula (I), under oxidative stress conditions, have an improved therapeutic index, compared with the precursor drugs.

For illustrative purposes the above mentioned tests are referred to the following compounds. See the Tables.

**Test 1: precursor drug: indomethacin**

- Maximum administrable dose to rats: 7.5 mg/Kg p.o. By administering a higher dose a toxicity is manifested, characterized by enteropathy, tremor, sedation until death (within 24 hours).
- The group of rats treated with NEM + indomethacin at the above mentioned dose shows gastrointestinal damages.

Since indomethacin in the groups treated with NEM causes gastrointestinal damages, it meets test 1. Indomethacin can therefore be used as a drug for preparing the compounds (I) and (II) of the present invention.

**Test 2: precursor drugs: indomethacin, paracetamol and mesalamine**

Indomethacin and paracetamol meet test 2 since the cellular damage (apoptosis) inhibition induced by CIP is not significantly different with respect to that of the controls.

Therefore the above drugs can be used as drugs for preparing the compounds (I) and (II) of the present invention.

On the contrary mesalamine does not meet test 2, since it inhibits the apoptosis induced by CIP. Therefore mesalamine according to test 2 could not be used as a precursor to prepare the compounds (I) and (II) of the present invention. It has been however found that mesalamine submitted to test 1 causes gastrointestinal damages.

Thus also mesalamine can be used as a precursor for preparing the compounds (I) and (II) of the present invention. Test 3 (L-NAME) precursors drugs: paracetamol, simvastatin, omeprazole

Paracetamol and simvastatin meet test 3 since they cause gastric and hepatic damages greater than those induced both by L-NAME + carrier and by the drug + carrier.

Therefore they can be used as precursors to prepare the compounds (I) and (II) of the present invention.

On the contrary it has been found that omeprazole neither causes gastric nor hepatic damages, nor influences blood-pressure. According to test 3 omeprazole could not be used as a precursor for preparing the compounds (I) and (II) of the present invention.

Test 4 (test for the compound precursor of B)

N-acetylcysteine in said test inhibits of 100% the production of radicals induced by DPPH. Since said percentage is higher than the limit of 50%, said drug cannot be used in the present invention as precursor of B.

4-Thiazolidin-carboxylic acid does not inhibit at any extent the production of radicals induced by DPPH (Table V). Thus the drug does not meet test 4 as requested by the instant invention and it could be used as a precursor of B if it meets test 5.

Test 5 (test for the compound precursor of B)

Table III relating to this test shows that the 4-thiazolidincarboxylic acid meets test 5 since the % inhibition is of 100%. Therefore the compound can be used as precursor of B.

Preferably in the invention compounds of formula (I), B contains free reactive functions, preferably selected from one or more of the following groups: XZ and  $Z_I-N-Z_{II}$  wherein  

$$\begin{array}{c} | \\ Z_I-N-Z_{II} \end{array}$$
X, Z,  $Z_I$  and  $Z_{II}$  are as above defined, or COOH, =NH.

When B contains free reactive functions it can suitably be reacted with the compounds having formula (III) wherein the free valence is saturated with a reactive group such as to be able to react with the free reactive function of B:



wherein:

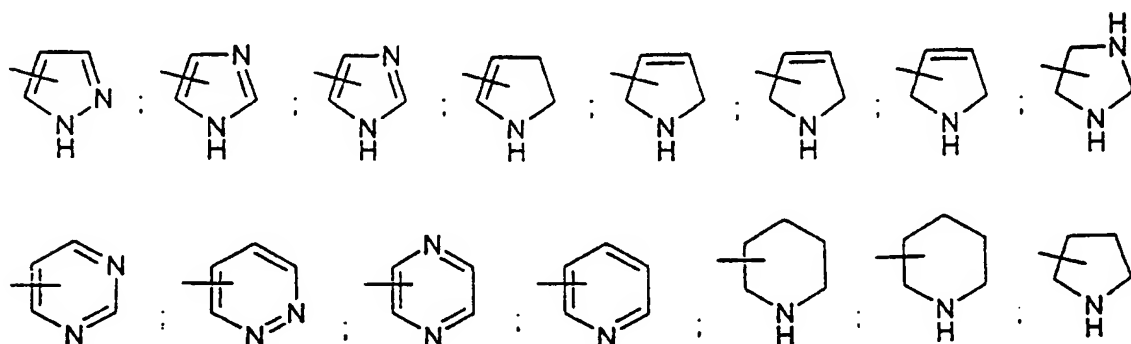
$n_{IX}$  is an integer between 0 and 3, preferably 1;

$R_{TIX}$ ,  $R_{TIX'}$ , equal to or different from each other are H or a linear or branched  $C_1-C_4$  alkyl; preferably  $R_{TIX}$ ,  $R_{TIX'}$ ,

are H.

$Y^3$  is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen atom, preferably one or two nitrogen atoms, said ring having 5 or 6 atoms. The  $Y^3$  ring can optionally have substituents, for example  $CH_2OH$ .

$Y^3$  in formula (III) is preferably selected from the following:



The most preferred of  $Y^3$  is Y12 (pyridyl).

The formula (I) compound salts are obtainable by reaction in organic solvent such as acetonitrile, tetrahydrofuran with an equimolecular amount of the corresponding organic or inorganic acid.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acids.

Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acids.

The derivatives according to the invention can be used in the therapeutic indications of the precursor drug, allowing to

obtain the advantages exemplified hereinafter for some groups of these drugs:

- Anti-inflammatory drugs NSAIDs: the invention compounds result very well tolerated and effective, even when the organism is debilitated and finds under conditions of oxidative stress. Said drugs can be used also in those pathologies wherein inflammation plays a significant pathogenetic role, such as for instance, but not limited to, in cancer, asthma, miocardic infarction.
- Adrenergic blockers, of  $\alpha$ - or  $\beta$ -blocker type: the action spectrum of the formula (I) compounds results wider than that of the starting drugs: to a direct action on the smooth musculature the inhibition of the nervous beta-adrenergic signals governing the contraction of the hematic ducts is associated. The side effects (dyspnoea, bronchoconstriction) affecting the respiratory apparatus are lower.
- Antithrombotic drugs: the antiplatelet activity is potentiated and in the case of the aspirin derivatives the gastric tolerability is improved.
- Bronchodilators and drugs active on the cholinergic system: the side effects affecting the cardio-vascular apparatus (tachycardia, hypertension) result lowered.
- Expectorants and mucolytic drugs: the gastrointestinal tolerability results improved.

- Diphosphonates: the toxicity relating to the gastrointestinal tract is drastically lowered.
- Phosphodiesterase (PDE) inhibitors (bronchodilators): the therapeutic efficacy is improved, the dosage being equal; it is therefore possible, using the compounds of the invention to administer a lower dose of the drug and reduce the side effects.
- Anti leukotrienic drugs: better efficacy.
- ACE-inhibitors: better therapeutic efficacy and lower side effects (dyspnoea, cough) affecting the respiratory apparatus.
- Antidiabetic drugs (insulin-sensitizing and hypoglycaemizing), antibiotic, antiviral, antitumoral, anticolitic drugs, drugs for the dementia therapy: better efficacy and/or tolerability.

The drugs which can be used as precursors in the general formula of the compounds of the invention are all those meeting at least one of the above mentioned tests 1, 2, 3. Examples of precursor drugs which can be used are the following:

For anti-inflammatory/analgesic drugs, the following can for example be mentioned:

anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, 5-amino-acetylsalicylic acid, alclofenac, alminoprofen, amfenac, bendazac, bermoprofen,  $\alpha$ -bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen,



cinmetacin, clidanac, clopirac, diclofenac sodium, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, oxaceprol, oxaprozin, oxyphenbutazone, parsalmide, perisoxal, phenyl acetylsalicylate, olsalazine, pyrazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicilamide O-acetic acid, salicylsulphuric acid, salsalate, sulindac, suprofen, suxibuzone, tenoxicam, tiaprofenic acid, tiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepirac, tomoxiprol;

analgesic drugs: acetaminophen, acetaminosalol, aminochlorthenoxazin, acetylsalicylic 2-amino-4-picoline acid, acetylsalicylsalicylic acid, anileridine, benoxaprofen benzylmorphine, 5-bromosalicylic acetate acid, bucetin, buprenorphine, butorphanol, capsaicine, cinchophen, ciramadol, clometacin, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimepheptanol, dipyroceryl, eptazocine, ethoxazene, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodone, hydromorphone, hydroxypethidine, ibu-

fenac, p-lactophenetide, levorphanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nicomorphine, norlevorphanol, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, phenocoll, phenoperidine, phenylbutazone, phenylsalicylate, phenylramidol, salicin, salicylamide, tiorphan, tramadol, diacerein, actarit;

for respiratory and urogenital apparatus drugs (bronchodilators and drugs active on the cholinergic system, expectorants/mucolytics, antiasthmatic/antiallergic antihistaminic drugs), the following can be mentioned:

bronchodilators and drugs active on the cholinergic system: acefylline, albuterol, bambuterol, bamifylline, bevonium methyl sulphate, bitolterol, carbuterol, clenbuterol, chlorprenaline, dioxethedrine, diphylline, ephedrine, epinephrine, eprozinol, etafredine, ethylnorepinephrine, etofylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetharine, isoprotenerol, mabuterol, metaproterenol, oxybutynin, oxitropium bromide, pirbuterol, procaterol, protokylol, proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-teobromineacetic acid, tiotropium bromide, tretoquinol, tulobuterol, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetra hydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromexine, domioldol, erdosteine, guaiacol, guaifenesin, iodinated glycerol,

letosteine, mesna, sobrerol, stepronin, terpin, tiopronin;

antiasthmatic/antiallergic antihistaminic drugs:  
acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam,  
chromoglycate, chromolyn, epinastine, fexofenadine,  
formoterol, histamine, hydroxyzine, levocabastine, lodoxamide,  
mabuterol, metron s, montelukast, nedocromil, repirinast,  
seratrodast, suplatast tosylate, terfenadine, tiaramide,  
urushiol, bromhexine;

for cardiovascular drugs (ACE-inhibitors, beta-blockers,  
antithrombotic and vasodilator drugs, antidiabetic and hypo-  
glycemic drugs), the following can be mentioned:

ACE-inhibitors: alacepril, benazepril, captopril, cero-  
napril, cilazapril, delapril, enalapril, enalaprilat, fo-  
sinopril, imidapril, lisinopril, losartan, moveltipril, na-  
phthopidil, perindopril, quinapril, ramipril, spirapril, temo-  
capril, trandolapril, urapidil;

beta-blockers: acebutolol, alprenolol, amosulalol, aroti-  
nolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol,  
bufuralol, bunitrolol, bupranolol, butofilol, carazolol, car-  
teolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol,  
esmolol, indenolol, labetalol, mepindolol, metipranolol,  
metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol,  
nipridalol, oxprenolol, penbutolol, pindolol, practolol,  
pronethalol, propranolol, sotalol, sulfinalol, talinolol, ter-  
tatolol, tilisolol, timolol, toliprolol, xibenolol;

antithrombotic and vasoactive drugs:      acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betahistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, dalteparin, dipyridamole, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, heparin, lamifiban, midrodine, nadroparin, nicotiny alcohol, nylidrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, papaveroline, reviparin sodium salt, ridogrel, suloctidil, tinofedrine, tinzaparin, triflusal, xanthinol niacinate;

antidiabetic drugs:    acarbose, carbutamide, glibornuride glybuthiazol(e), miglitol, repaglinide, troglitazone, 1-butyl-3-metanyl-urea, tolrestat, nicotinamide;

for antitumoral drugs, the following can be mentioned: ancitabine, anthramycin, azacitidine, azaserine, 6-azauridine, bicalutamide, carubicin, carzinophilin, chlorambucil, chlorozotocin, cytarabine, daunorubicin, defosfamide, demecolcine, denopterin, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicin, droloxifene, edatrexate, eflornithine, enocitabine, epirubicin, epitiostanol, etanidazole, etoposide, fenretinide, fludarabine, fluorouracil, gemcitabine, hexestrol, idarubicin, lonidamine, mannomustine, melphalan, menogaril, 6-mercaptopurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, mycophenolic acid, ninopterin, nogalamycin, paclitaxel, pentostatin, pira-

rubicin, piritrexim, plicamycin, podophyllic acid, porfimer sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, thiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicin;

for antiulcer drugs the following can be mentioned:  $\epsilon$ -acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecbet, enprostil, esaprazole, irsogladine, misoprostol, omeprazole, ornoprostil, pantoprazole, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil;

among anti-hyperlipidemic drugs (statines) the following can be mentioned: atorvastatin, cilastatin, dermostatin, fluvastatin, lovastatin, mevastatin, nystatin, pentostatin, pepstatin, privastatin sodium, simvastatin;

among antibiotic/antiviral drugs the following can be mentioned:

antibiotics: amdinocillin, amoxicillin, ampicillin, apalcillin, apicycline, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoypas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefopera-

zone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephradine, cephaloridine, cephalosporin C, cephalothin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephapirin sodium, cephradine, chloramphenicol, chlortetracycline, cinoxacin, clavulanic acid, clometocillin, cloxacillin, cyclacillin, cycloserine, demeclocycline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacillin, hetacillin, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, meclocycline, meropenem, metampicillin, methacycline, methicillin sodium, mezlocillin, minocycline, moxalactam, mupirocin, myxin, negamycin, novobiocin, oxacillin, panipenem, penicillin G potassium salt, penicillin N, penicillin O, penicillin V, phenethicillin potassium salt, pipacycline, piperacillin, pirlimycin, porfirimycin, propycillin, quinacillin, ritipenem, rolitetracycline, sancycline, sedecamycin, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidin, azithromycin, clarithromycin, dirithromycin, enviomycin, erythromycin, josamycin, midecamycin, miokamycin, oleandomycin, rifabutin, rifamide, rifamycin, rifaximin, rokitamycin, spiramycin, troleandomycin, viomycin, virginiamycin;

amikacin, apramycin, arbekacin, dibekacin, dihydrostreptomycin,

fortimicins, gentamicin, micronomicin, neomycin, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin;

bacampicillin, cefcapene pivoxil, cefpodoxime proxetil, panipenem, pivampicillin, pivcefalexin, sultamicillin, talampicillin;

carbomycin, clindamycin, lincomycin, mikamycin, rosaramicin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, flumequine, grepafloxacin, lomefloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rifloxacin, sparfloxacin, tosufloxacin, trovafloxacin, clomocycline, guamecycline, oxytetracycline, nifurpirinol, nifurprazine; p-aminosalicylic acid, p-aminosalicylic acid hydrazide, clofazimine, deoxydihydrostreptomycin, ethambutol, glyconiazide, isoniazid, opiniazide, phenyl aminosalicylate, rifampin, rifapentine, salinazid, 4-4'-sulfynyldianiline, Acediasulfone, dapsone, succisulfone, p-sulfanilylbenzylamine, thiazolsulfone, acetyl sulfamethoxypyrazine, mafenide, 4'-(methylsulfamoyl)sulfanilanilide, salazosulfadimidine, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine,

sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 2-p-sulfanilylanilinoethanol, N<sup>4</sup>-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfisomidine, sulfisoxazole, 4-sulfanilamido salicylic acid; negamycin, carumonan, cloxyquin, nitroxoline, arginine, metronidazole;

antiviral drugs: acyclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxin, ribavirin, rimantadine, saquinavir, sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;

among bone resorption inhibitors (diphosphomates) the following can be mentioned: alendronic acid, butedronic acid, etidronic acid, oxidronic acid, pamidronic acid, risedronic acid;

among antidementia drugs the following can be mentioned: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

The preferred substances are the following:

among anti-inflammatories: acetylsalicylic acid, 5-



aminoacetylsalicylic acid, carprofen, diclofenac sodium, diflunisal, etodolac, flufenamic acid, flunixin, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, naproxen, niflumic acid, olsalazine, piroxicam, salsalate, sulindac, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, tolmetin, zomepirac, tomoxiprol;

among analgesic drugs: acetaminophen, acetylsalicylsalicylic acid, benoxaprofen, buprenorphine, butorphanol, capsaicin, diacerein, dihydrocodeine, ethylmorphine, eugenol, phenylbutazone, meptazinol, morphine, nalbuphine, pentazocine, thiorphan, tramadol, actarit;

among respiratory and urogenital apparatus drugs: (bronchodilators, drugs active on the cholinergic system, expectorants/mucolytics, antiasthmatics/antiallergic antihistaminic drugs):

bronchodilators and drugs active on the cholinergic system : albuterol, carbuterol, clenbuterol, difylline, etofylline, fenoterol, ipratropium bromide, metaproterenol, oxybutynin, pirbuterol, salmeterol, terbutaline, tiotropium bromide, zaprinast, cyclo-drine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetrahydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromexine, guaia-col, sobrerol;

antiasthmatic/antiallergic antihistaminic drugs:

cetirizine, chromoglycate, histamine, levocabastine, lodoxamide, montelukast, terfenadine, bromexine.

Among cardiovascular drugs:

ACE-inhibitors: captopril, enalapril, lisinopril, losartan, ramipril;

beta blockers: alprenolol, atenolol, bupranolol, labetalol, metipranolol, metoprolol, pindolol, propranolol, timolol;

antithrombotic and vasoactive drugs: acetylsalicylic acid, acetorphan, argatroban, clopidogrel, dalteparin, dipyridamole, enoxaparin, heparin, iloprost, midodrine, ozagrel, phenylpropanolamine trifusal;

antidiabetic drugs: tolrestat, nicotinamide;

among antitumoral drugs: anthramycin, daunorubicin, doxorubicin, epirubicin, fluorouracil, methotrexate, vinblastine;

among antiulcer drugs: cimetidine, omeprazole, pantoprazole;

among antihyperlipidemic drugs: lovastatin, pravastatin sodium, simvastatin;

among antibiotic/antiviral drugs:

antibiotic drugs: amoxicillin, ampicillin, aztreonam, biapenem, carbenecillin, cefaclor, cefadroxil, cefamandole, cefatrizine, cefoxitin, clavulanic acid, dicloxacillin, imipenem, meclocycline, methacycline, moxalactam, panipenem, sul-

bactam, azithromycin, erythromycin, josamycin, miokamycin, rifabutine, rifamide, rifamycin, gentamicin, paromomycin, sisomicin, bacampicillin, carbomycin, clindamycin, ciprofloxacin, clinafloxacin, difloxacin, enrofloxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pipemidic acid,

apicycline, clomocycline, oxytetracycline, nifurpirinol, nifurprazine, isoniazid, rifampin, rifapentine, dapsone, thiazolsulfone, sulfamethoxazole, sulfamoxole, metronidazole, arginine;

antiviral drugs: acyclovir, famciclovir, ganciclovir, penciclovir, ribavirin, vidarabine, zidovudine;

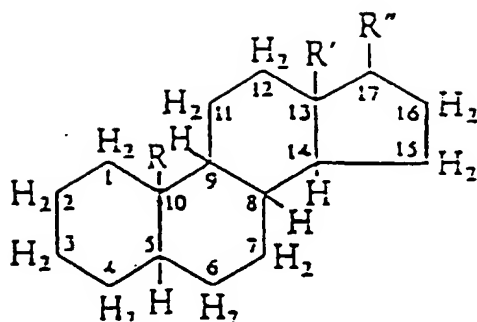
among bone resorption inhibitors: alendronic acid, etidronic acid, pamidronic acid;

among antimentia drugs: oxiracetam, tacrine, velnacrine.

The above mentioned substances, R precursors, are prepared according to the methods known in the prior art. See for example in "The Merck Index, 12a Ed. (1996), herein incorporated by reference. When available, the corresponding isomers, comprising optical isomers, can be used.

Tomoxiprol is obtained according to the method described in EP 12,866.

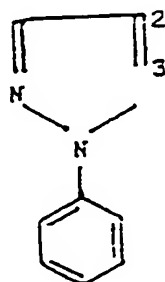
The steroidal compounds wherein A = R—, have the following structure:



wherein in substitution of the hydrogens of the CH groups or of the two hydrogens of the CH<sub>2</sub> groups mentioned in the general formula, the following substituents can be present:

in position 1-2: there may be a double bond;

in position 2-3: there may be the following substituent:



in position 2: there may be Cl, Br;

in position 3: there may be CO, -O-CH<sub>2</sub>-CH<sub>2</sub>-Cl, OH;

in position 3-4: there may be a double bond;

in position 4-5: there may be a double bond;

in position 5-6: there may be a double bond;

in position 5-10: there may be a double bond;

in position 6: there may be Cl, F, CH<sub>3</sub>, -CHO;

in position 7: there may be Cl, OH;

in position 9: there may be Cl, F;

in position 11: there may be OH, CO, Cl, CH<sub>3</sub>;

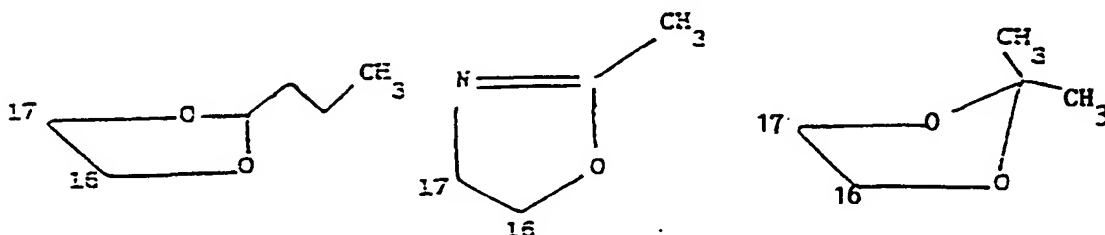
in position 16: there may be CH<sub>3</sub>, OH, =CH<sub>2</sub>;

in position 17: there may be OH, CH<sub>3</sub>, OCO(O)<sub>ua</sub>(CH<sub>2</sub>)<sub>va</sub>CH<sub>3</sub>, C≡CH or



wherein ua is an integer equal to 0 or 1, va is an integer from 0 to 4;

in position 16-17: there may be the following groups:

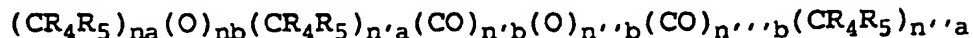


R and R', equal to or different from each other, can be hydrogen or linear or branched alkyls from 1 to 4 carbon atoms, preferably R = R' = CH<sub>3</sub>;

R" is  $-(\text{CO-L})_t-(\text{L})_{t2}-(\text{X}_0^{\text{I}})_{t1}-$

wherein t, t1 and t2 are integers equal to or different from each other equal to 0 or 1, with the proviso that when t = 0 t2 = 1 and when t = 1 t2 = 0, and that t and t1, or t2 and t1, cannot contemporaneously be equal to 0 when A does not contain -OH groups;

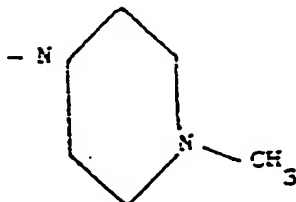
the bivalent bridging group L is selected from:



wherein na, n'a, and n''a, equal to or different from each other, are integers from 0 to 6, preferably 1-3; nb, n'b, n''b and n'''b, equal to or different from each other, are integers equal to 0 or 1; R<sub>4</sub>, R<sub>5</sub>, equal to or different from each other,

are selected from H, linear or branched alkyl from 1 to 5 carbon atoms, preferably from 1 to 3;

$X_0^I$  is X as above defined, or equal to  $X_2^I$  wherein  $X_2^I$  is equal to OH,  $CH_3$ , Cl,  $N(-CH_2-CH_3)_2$ ,  $SCH_2F$ , SH, or



Preferably  $R'' = -CO-CH_2OH$ ,  $-CH(CH_3)-CH_2-CH_2-COOH$ .

In the precursor steroids those having the hydroxyl function in position 3 and/or in position 11, and/or having in  $R''$  an hydroxyl or carboxylic function in terminal position, are preferred.

The precursor steroids of A which can be mentioned and which are preferred, are those listed hereinunder, obtainable according to the processes known in the art.

As precursors and respective processes, those for example described in The Merck Index, ed. 12 of 1996, herein incorporated by reference, can be mentioned. The precursors (according to the Merck nomenclature) are the following, wherein  $H_2$ , H, R,  $R'$ ,  $R''$  have the meaning mentioned in the compounds listed herein: Budesonide, Hydrocortisone, Alclomethasone, Algestone, Beclomethasone, Betamethasone, Chloroprednisone, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Cortisone, Corticosterone, Deflazacort, Desonide, Desoxi-

methasone, Dexamethasone, Diflorasone Diflucortolone, Diflu-prednate, Fluazacort, Flucloronide, Flumethasone, Flunisolide, Fluocinolone Acetonide, Fluocinonide, Fluocortyn Butyl, Fluocortolone, Fluorometholone, Fluperolone Acetate, Fluprednidene Acetate, Fluprednisolone, Flurandrenolide, Formo-cortal, Halcinonide, Halobetasol Propionate, Halomethasone, Halopredone Acetate, Hydrocortamate, Loteprednol Etabonate, Medrysone, Meprednisone, Methylprednisolone, Momethasone Furoate, Paramethasone, Prednicarbate, Prednisolone, Prednisolone 25-Diethylaminoacetate, Prednisolone Sodium Phosphate, Prednisone, Prednival, Prednylidene, Rimexolone, Triamcinolone, Triamcinolone Acetonide, 21-Acetoxypregnenolone, Cortivazol, Amcinonide, Fluticasone Propionate, Mazipredone, Tixocortol, Triamcinolone Hexacetonide, Ursodesoxycholic acid, Chenodeoxycholic acid, Mitatrienediol, Moxestrol, Ethynylestradiol, Estradiol, Mestranol.

The formula (I) compounds are prepared as mentioned hereinafter.

If the reactive function of the drug (for example -COOH, -OH) is involved in a covalent bond, for example of ester, amide, ether type, said function can be restored with the methods well known in the prior art.

The reactions used for obtaining the formula (I) compounds are reactions leading to the formation of bonds for example of ester, amide, thioester type well known to the skilled in the

field.

If in the two compounds of the reaction other functional groups COOH and/or HX wherein X is as above defined are present, they must be protected before the reaction according to the methods known in the prior art; for example as described in the paper by Th. W. Greene: "Protective groups in organic synthesis", Harward University Press, 1980.

When in the radical B there is a second reactive function, of XZ and  $Z_I-N-Z_{II}$  type wherein X, Z,  $Z_I$  and  $Z_{II}$  are as above defined, or a COOH, =NH function, it is possible to bind to B a radical corresponding to the formula (III), wherein the free valence is saturated with a reactive function such as to be combined with the second reactive function of B. Also in this case the reactions are those commonly used in the prior art.

The obtained compound is reacted with the drug precursor.

The compounds object of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral and topic use according to the well known methods of the prior art, along with the usual excipients; see for example the paper "Remington's Pharmaceutical Sciences 15a Ed."

The amount on a molar basis of the active principle in these formulations is the same, or lower, compared with that used of the corresponding precursor drug.

The daily administrable doses are those of the precursor

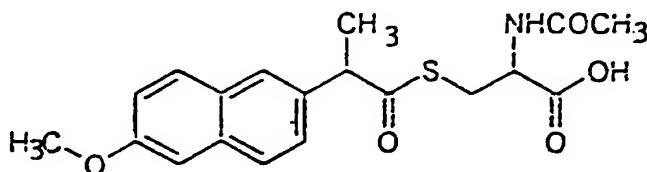


drugs, or in case lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk reference".

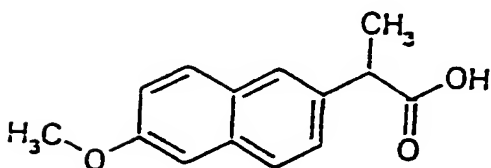
The following examples have the purpose to illustrate the invention and are not to be considered as limitative of the same.

#### EXAMPLE 1

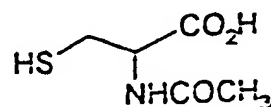
Synthesis of (S,S)-N-acetyl-S-(6-methoxy- $\alpha$ -methyl-2-naphthalen acetyl)cysteine having the formula



The precursor is naproxene (Formula VI), the precursor of B is N-acetylcysteine of formula (CVIII)



(VI)



(CVIII)

a) Synthesis of (S,S)-N-acetyl-S-(6-methoxy- $\alpha$ -methyl-2-naphthalen acetyl)cysteine

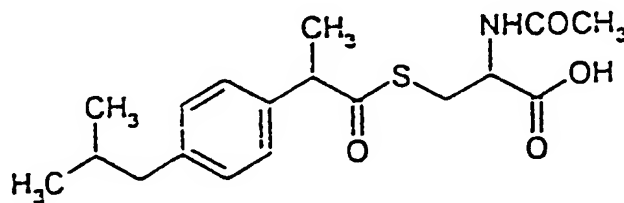
To a solution of 6-methoxy- $\alpha$ -methyl-2-naphthalenacetic acid (10 g, 43.4 mmols) in chloroform (100 ml) and N,N-dimethylformamide (6 ml), 1,1'-carbonyldiimidazole (7.04 g, 43.4

mmoles) is added. After 15 minutes the obtained solution is treated with (S)-N-acetylcysteine (7.08 g, 43.4 mmoles) and left at room temperature for 12 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine. The organic phase is anhydriified with sodium sulphate and then evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with ethyl acetate. 11.66 g of the expected product are obtained in the form of a white solid having m.p. 122°-126°C.

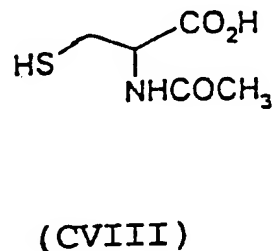
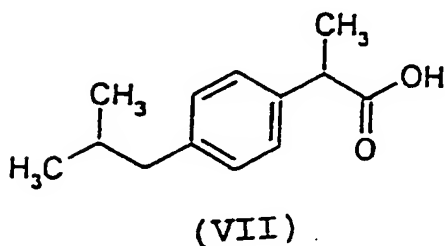
<sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.71-7.65 (3H, m), 7.34 (1H, dd), 7.16-7.09 (2H, m), 6.36 (1H, d), 4.67 (1H, m), 4.00 (1H, q), 3.90 (3H, s) 3.32 (2H, t), 1.84 (3H, s), 1.59 (3H, d).

#### EXAMPLE 2

Synthesis of (S)-N-acetyl-S-{α-methyl[4-(2-methylpropyl) benzene] acetyl}cysteine having formula



The precursor is ibuprofen of formula VII, the precursor of B is N-acetylcysteine of formula (CVIII)



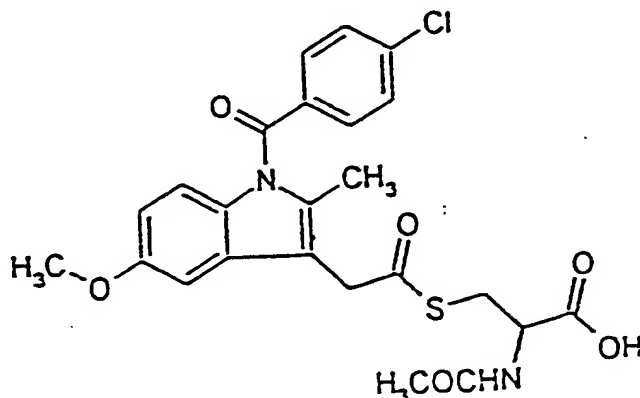
a) Synthesis of (S)-N-acetyl-S- $\{\alpha$ -methyl[4-(2-methylpropyl)benzene]acetyl}cysteine

To a solution of  $\alpha$ -methyl[4-(2-methylpropyl)benzene] acetic acid (10 g, 48.48 mmol) in chloroform (100 ml) and N,N-dimethylformamide (6 ml) 1,1'-carbonyldiimidazol (7.86 g, 48.48 mmol) is added. After 1 hour the obtained solution is treated with (S)-N-acetylcysteine (7.91 g, 48.47 mmol) and left at room temperature for 24 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine. The organic phase is anhydriified with sodium sulphate and then evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with ethyl acetate. 13.3 g of the expected product are obtained in an oil form.

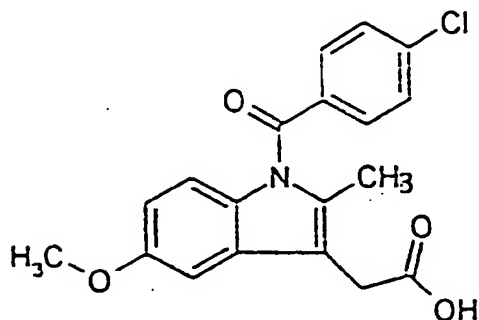
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 10.17 (1H, s) 7.13 (2H, d) 6.54 (1H, d), 4.76 (1H, m), 3.93 (1H, q), 3.42-3.30 (2H, m), 2.49 (2H, d), 1.85-1.83 (4H, m), 1.55 (3H, d), 0.93 (6H, d).

EXAMPLE 3

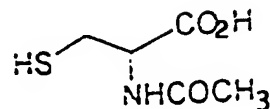
Synthesis of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cysteine having formula



The precursor is indomethacin of formula (VIII), the precursor of B is N-acetylcysteine of formula (CVIII)



(VIII)



(CVIII)

a) Synthesis of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cysteine

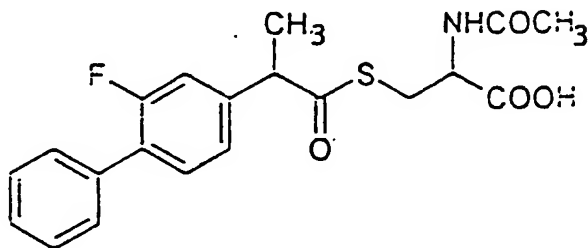
To a solution of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid (10 g, 28.00 mmol) in chloroform (100 ml) and N,N-dimethylformamide (2 ml) 1,1'-carbonyldiimidazol (4.53 g, 28.00 mmol) is added. After 1 hour the obtained solution is treated with (S)-N-acetylcysteine (4.56 g, 28.00 mmol) and left at room temperature for 24 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine. The organic phase is anhydriified with sodium sulphate and then evaporated at reduced pressure. The obtained residue is purged by chromatography on silica gel eluting with ethyl acetate. 7.79 g of the expected product are obtained in the form of a yellow solid having m.p. 129°C.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 12.90 (1H, s), 8.21 (1H, d), 7.69-7.64

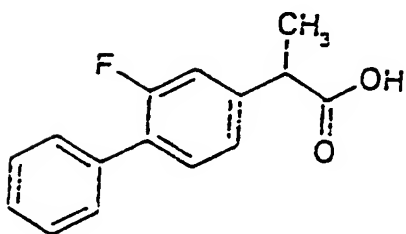
(4H, m), 7.06 (1H, d), 6.96 (1H, d), 6.73 (1H, dd), 4.33 (1H, m), 4.02 (2H, s), 3.77 (3H, s), 3.33-2.96 (2H, m), 2.22 (3H, s), 1.78 (3H, s).

EXAMPLE 4

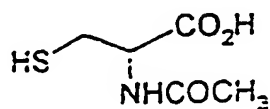
Synthesis of (S)-N-acetyl-[2-fluoro- $\alpha$ -methyl-(1,1'-biphenyl)-4-acetyl]cysteine having formula



The precursor is flurbiprofen of formula (IX), the precursor of B is N-acetylcysteine of formula (CVIII)



(IX)



(CVIII)

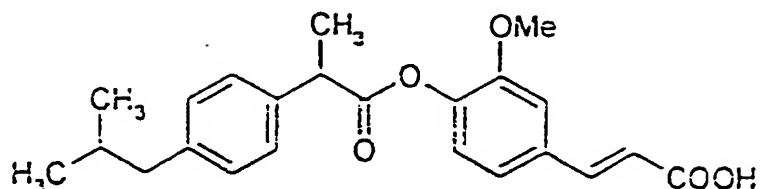
The compound is synthesized according to the process described in Example 1. The compound looks as an oil. Yield: 70%

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 8.38 (1H, d), 7.67-7.50 (6H, m), 7.49-7.53 (2H, m), 4.52-4.41 (1H, m), 4.22 (1H, q), 3.50-3.10 (2H, m), 1.92 (3H, s), 1.58 (3H, d).

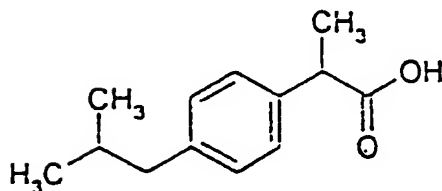
EXAMPLE 5

Preparation of trans-3-[4-[ $\alpha$ -methyl-[4-(-2-methylpropyl)benze-

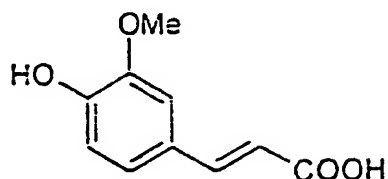
ne] acetyloxy]-3-methoxyphenyl]-2-propenoic acid having formula:



The precursor is ibuprofen of formula (VII), the precursor of B is ferulic acid of formula (DII):



(VII)



(DII)

a) Synthesis of the trans-3-[4-[α-methyl-4-(2-methylpropyl)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoic acid

To a solution of α-methyl-4-(2-methylpropyl)benzene]acetic acid (5.03 g, 24.4 mmol) in tetrahydrofuran (100 ml) and N,N-dimethylformamide (5 ml) 1,1-carbonyldiimidazole (4.25 g, 24.8 mmol) is added. After 1 hour the obtained solution is treated with ferulic acid (4.90 g, 25 mmol), sodium ethylate (89 mg) is added and then it is left at room temperature under stirring for 12 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine. The organic phase is anhydriified with sodium sulphate and evaporated at reduced

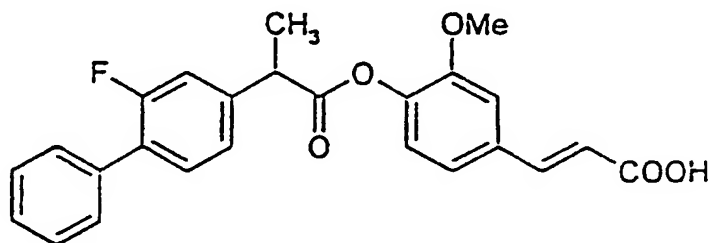
pressure.

The obtained residue is purified by chromatography on silica gel, eluting with ethyl acetate/n-hexane 7/3. 5.1 g of trans-3-[4-[ $\alpha$ -methyl-[4-(-2-methylpropyl)benzene] acetyl]-3-methoxyphenyl]-2-propenoic acid are obtained as a white solid, having m.p. 131°-137°C.

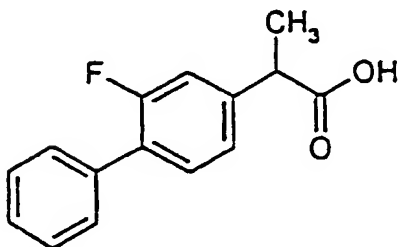
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 7.72 (1H, d), 7.32 (2H, dd), 7.26 (1H, m), 7.16-7.07 (4H, m), 6.98 (1H, d), 6.37 (1H, d), 3.99 (1H, q), 3.73 (3H, s), 2.47 (2H, d), 1.88 (1H, m), 1.63 (3H, d), 0.92 (6H, d).

#### EXAMPLE 6

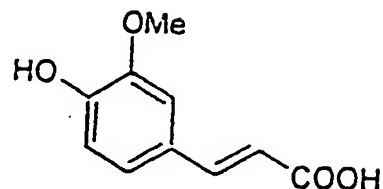
Synthesis of trans-3-[4-[2-fluoro- $\alpha$ -methyl-(1,1'-biphenyl)-4-acetyloxy]-3-methoxyphenyl]-2-propenoic acid having formula:



The precursor is flurbiprofen of formula (IX), the precursor of B is ferulic acid of formula (DII)



(IX)



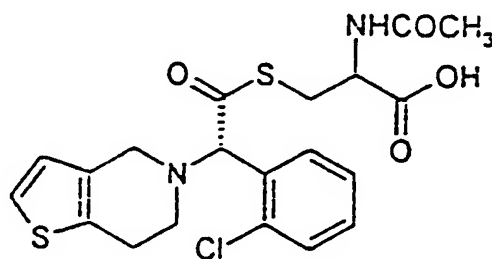
(DII)

The compound is synthesized according to the process described in Example 5. The total process yield is 60%. The compound looks as an amorphous solid.

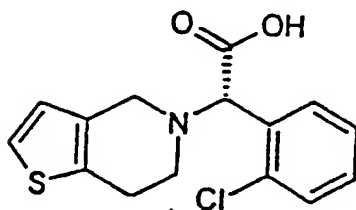
$^1\text{H}$ - NMR ( $\text{CDCl}_3$ ): 7.75 (1H, d), 7.52 (2H, m), 7.46-7.26 (4H, m) 7.26 (3H, m), 7.05 (2H, m), 7.00 (1H, d), 6.37 (1H, d), 4.03 (1H, q), 3.77 (3H, s), 1.65 (3H, d).

#### EXAMPLE 7

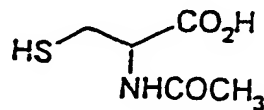
Preparation of N-acetyl-S-[(S)- $\alpha$ -(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)acetyl] (S)-cysteine



wherein the precursor is clopidogrel having formula (XI) and the precursor of B is N-acetylcysteine having formula (CVIII):



(XI)



(CVIII)

The compound is synthesized following the procedure reported in Example 1. The yield is 51%.



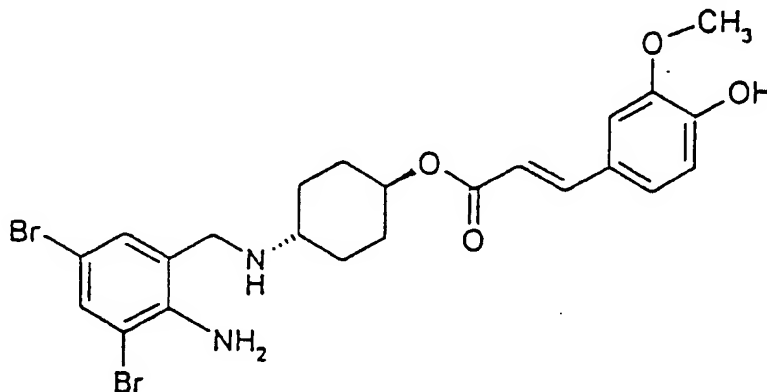
Elementary analysis:

Calculated C: 53.03% H: 4.67% N: 6.18% S: 14.16% Cl: 17.82%

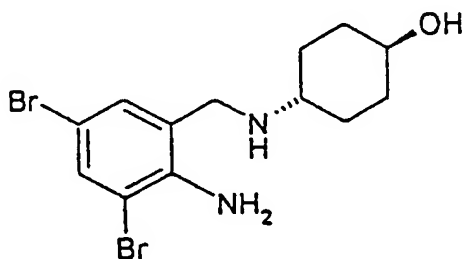
Found C: 53.00% H: 4.63% N: 6.15% S: 14.10% Cl: 17.87%

#### EXAMPLE 8

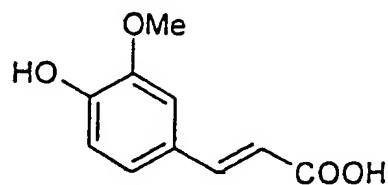
Preparation of [3-methoxy-4-hydroxyphenyl]-2-trans-propenoyl-4-[(2-amino-3,5-dibromophenyl)methylamino] cyclohexanol ester



wherein the precursor is ambroxol having formula (XII) and the precursor of B is represented by ferulic acid having formula (DII):



(XII)



(DII)

a) Synthesis of 4-[(2-tert-butoxycarbonylamino-3,5-dibromophenyl)methylamino] trans cyclohexanol

To a mixture of 4-[(2-amino-3,5-dibromophenyl)methylamino]cyclohexanol (5 g, 13.22 mmols) in dioxane (35 ml) and

water (50 ml), triethylamine (3.31 ml, 23.7 mmol) and di-tert-butylidicarbonate (3.46 g, 15.86 mmol) are added under stirring. After 24 hours the solution is concentrated under vacuum, a HCl 1% solution until neutral pH (pH=7) is added and the organic phase is extracted with ethyl acetate. The organic phase is anhydriified with sodium sulphate and evaporated under vacuum. 4-[(2-tert-butoxycarbonylamino-3,5-dibromophenyl)methyl amino]cyclohexanol is obtained which is used without further purification.

b) Synthesis of (3-methoxy-4-hydroxyphenyl)-2-trans-propenoyl-4-[(2-tert-butoxycarbonylamino-3,5-dibromophenyl)methylamino]cyclohexanol ester

To a solution of ferulic acid (4 g, 20.5 mmol) in tetrahydrofuran (40 ml) cooled at 0°C, 1,1'-carbonyldiimidazole (3.34 g, 20.5 mmol) is added. After 10 minutes the solution is treated with 4-[(2-ter-butoxycarbonylamino-3,5-dibromophenyl)methyl amino]cyclohexanol (9.8 g, 20.5 mmol) and let react at room temperature for 4 hours. The reaction mixture is concentrated under vacuum, treated with methylene chloride, washed with a HCl 1% solution and then with water. The organic phase is anhydriified with sodium sulphate and then evaporated under vacuum. The obtained residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 1/1. (3-methoxy-4-hydroxyphenyl)-2-trans propenoyl 4-[(2-tert-butoxycarbonylamino-3,5-dibromo phenyl)methylamino]

cyclohexanol ester, is obtained.

c) Synthesis of [3-methoxy-4-hydroxyphenyl]-2-trans propenoyl-4-[(2-amino-3,5-dibromo-phenyl)methylamino] cyclohexanol ester

To a solution of (3-methoxy-4-hydroxyphenyl)-2-trans propenoyl-4-[(2-ter-butoxycarbonylamino-3,5-dibromo-phenyl)-methylamino] cyclohexanol ester (2 g, 3.06 mmoles) in ethyl acetate (50 ml), cooled at 0°C and kept under stirring, a 5N HCl solution in ethyl acetate (3.17 ml) is added. Lastly the precipitate is filtered. The obtained crude product is treated with ethyl acetate, to which a 5% sodium bicarbonate solution is added. The mixture is shaken and the bicarbonate solution is replaced with an equal part of water. The mixture is shaken again, the organic phase is recovered, anhydrified with sodium sulphate and evaporated at reduced pressure. [3-methoxy-4-hydroxyphenyl]-2-transpropenoyl 4-[(2-amino-3,5-dibromo phenyl)methylamino] cyclohexanol ester is obtained. Yield: 41%.

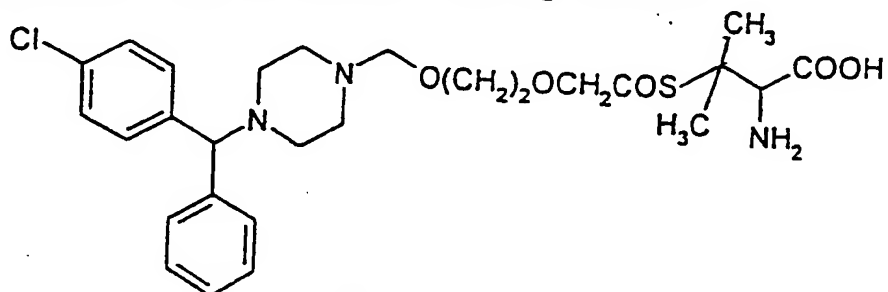
Elementary analysis:

Calculated C: 50.90% H: 4.62% N: 4.94% Br: 28.22%

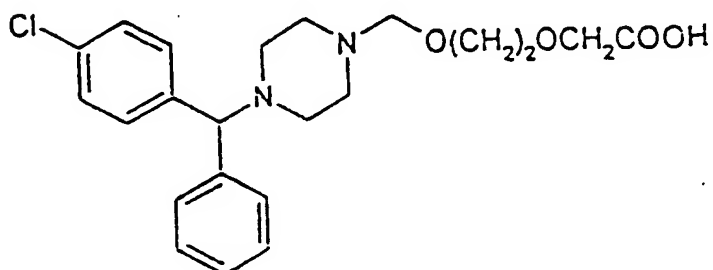
Found C: 50.81% H: 4.63% N: 4.89% Br: 28.18%

#### EXAMPLE 9

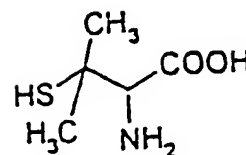
Preparation of S-[[2-[4-(4-chlorophenyl)phenylmethyl)-1-piperazinyl]ethoxy]acetyl] penicillamine having formula



wherein the precursor is cetirizine of formula (XIV) and the precursor of B is penicillamine (formula CV):



(XIV)



(CV)

a) Synthesis of S-[[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetyl] N-tert-butoxycarbonylpenicillamine

The compound is prepared according to the method reported in Example 1, using N-tert-butoxycarbonyl-penicillamine instead of N-acetyl cysteine.

b) Synthesis of S-[[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetyl]-penicillamine

The compound is obtained from the previous one by following the method described in step c) of Example 8 in order to remove the protective group N-tert-butoxycarbonyl and recover the aminic function. Yield: 29%.

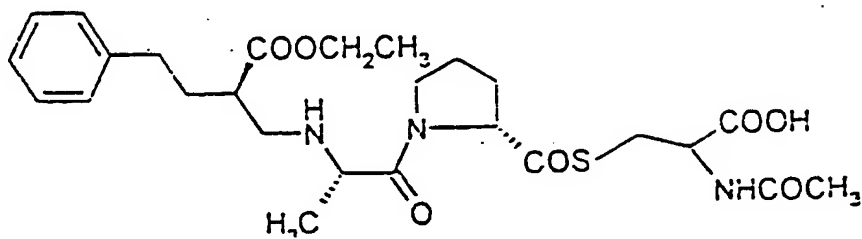
Elementary analysis:

Calculated C: 58.96% H: 6.59% N: 7.63% S: 5.83% Cl: 16.44%

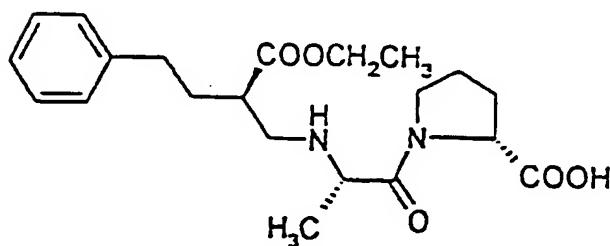
Found C: 58.89% H: 6.50% N: 7.58% S: 5.79% Cl: 16.40%

EXAMPLE 10

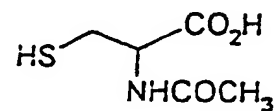
Preparation of N-acetyl-S-[(S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-prolin]cysteine



wherein the precursor is enalapril of formula (XV) and the precursor of B is N-acetylcysteine (formula CVIII):



(XV)



(CVIII)

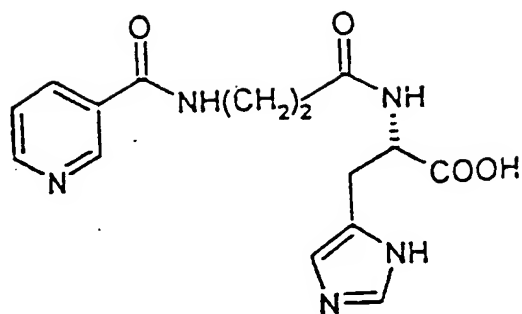
The compound is synthesized following the method reported in Example 1. Yield: 35%

Elementary analysis:

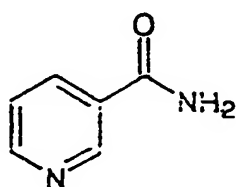
Calculated	C: 58.30%	H: 6.96%	N: 7.84%	S: 5.98%
Found	C: 58.25%	H: 6.94%	N: 7.88%	S: 5.87%

EXAMPLE 11

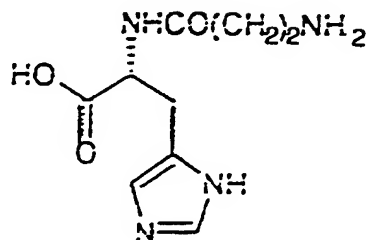
Preparation of N-nicotinoyl-β-alanyl (L)-histidine



wherein the precursor is nicotinamide of formula (XXIII) and the precursor of B is carnosine (formula CI):



(XXIII)



(CI)

a) Synthesis of N-nicotinoyl- $\beta$ -alanyl (L)-histidine

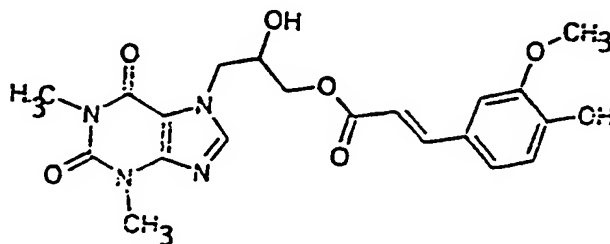
To a solution of nicotinic acid (2.5 g, 20.5 mmol) in tetrahydrofuran (40 ml) cooled at 0°C, 1,1'-carbonyldiimidazol (3.34 g, 20.5 mmol) is added under stirring. After 10 minutes to the solution (L)-carnosine (4.6 g, 20.5 mmol) is added and it is left under stirring at room temperature for 4 hours. The reaction mixture is concentrated under vacuum, treated with methylene chloride, washed with HCl 1% and then with water. The organic phase is anhydriified with sodium sulphate and evaporated under vacuum. The obtained residue is chromatographed on silica gel column, eluting with ethyl acetate. N-nicotinoyl- $\beta$ -alanyl (L)-histidine is recovered. Yield 45%.

Elementary analysis:

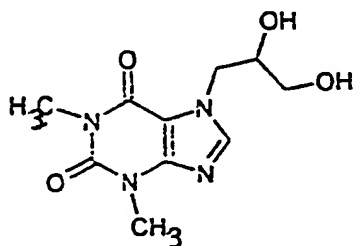
Calculated	C: 54.49%	H: 4.88%	N: 21.27%
Found	C: 54.30%	H: 5.00%	N: 21.30%

### EXAMPLE 12

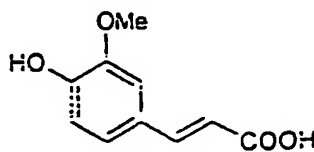
Preparation of 7-[2-hydroxy-3-[3-methoxy-5-hydroxybenzoyl]trans-2-propenoyl]theophylline



wherein the precursor is the diphylline of formula (XXVI) and the precursor of B is the ferulic acid (formula DII):



(XXVI)



(DII)

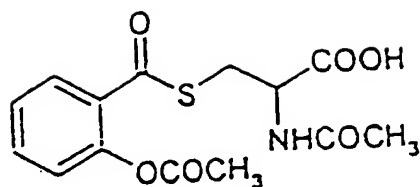
The drug is synthesized according to the process described in Example 8. Yield: 28%

Elementary analysis:

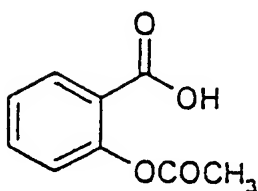
Calculated	C: 57.66%	H: 5.32%	N: 10.13%
Found	C: 57.70%	H: 5.37%	N: 10.11%

### EXAMPLE 13

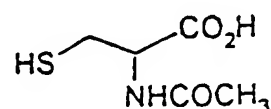
Preparation of N-acetyl-S-(2-acetylbenzoyl)cysteine of formula



wherein the precursor is acetylsalicylic acid of formula (XXVII) and the precursor of B is N-acetylcysteine (formula CVIII):



(XXVII)



(CVIII)

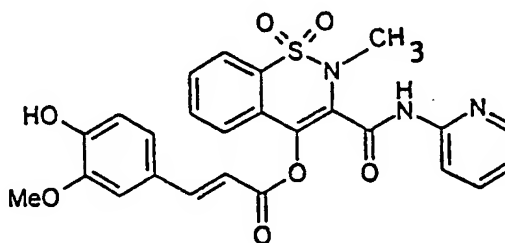
The compound is synthesized according to the process described in Example 1. Yield 63%.

#### Elementary analysis

Calculated	C: 51.69%	H: 4.65%	N: 4.31%	S: 9.86%
Found	C: 51.64%	H: 4.68%	N: 4.33%	S: 9.89%

#### EXAMPLE 14

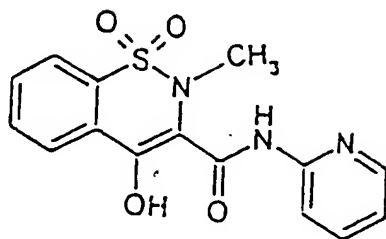
Preparation of 4-[3-[3-methoxy-5-hydroxyphenyl]-2-propenoyloxy]-2-methyl-N-2-pyridinyl-2H-1,2-benzothiazin-3-carboxamide-1,1-dioxide



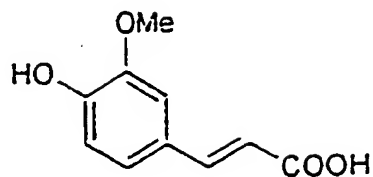
wherein the precursor is piroxicam of formula (XXVIII) and the



precursor of B is ferulic acid (formula DII):



(XXVIII)



(DII)

The compound is synthesized according to the process reported in Example 8. Yield 25%.

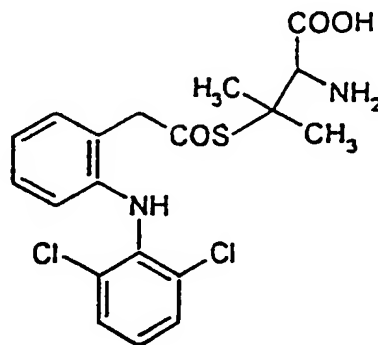
Elementary analysis

Calculated C: 59.14% H: 4.17% N: 8.31% S: 6.31%

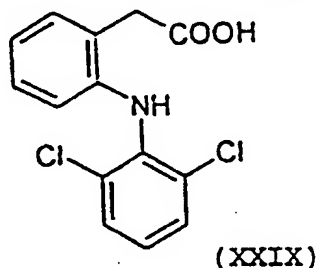
Found C: 59.01% H: 4.09% N: 8.20% S: 6.21%

#### EXAMPLE 15

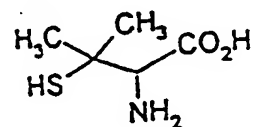
Preparation of S-[2-[(2,6-dichlorophenyl)amino]benzeneacetyloxy]penicillamine of formula



wherein the precursor is diclofenac of formula (XXIX) and the precursor of B is penicillamine (formula CV):



(XXIX)



(CV)

The compound is synthesized according to the process described in Example 9. Yield 53%.

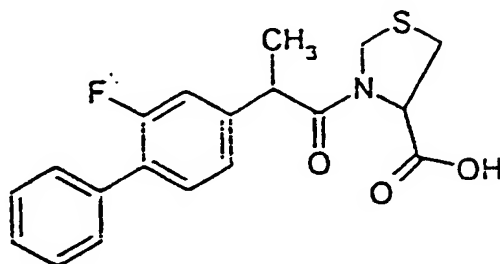
Elementary analysis

Calculated C: 49.88% H: 3.66% N: 7.30% S: 8.32% Cl: 18.40%

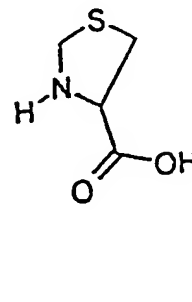
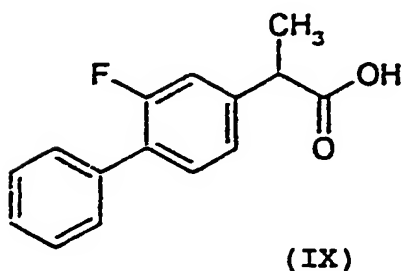
Found C: 49.90% H: 3.64% N: 7.29% S: 8.25% Cl: 18.35%

#### EXAMPLE 16

Synthesis of the 3-[2-fluoro- $\alpha$ -methyl-(1,1'-biphenyl)-4-acetyl]thiazolidin-4-carboxylic acid



starting from flurbiprofen of formula (IX), the precursor of B is (L)-4-thiazolidin carboxylic acid of formula (PIV)



a) Synthesis of the 3-[2-fluoro- $\alpha$ -methyl-(1,1'-biphenyl)-4-acetyl]thiazolidin-4-carboxylic acid

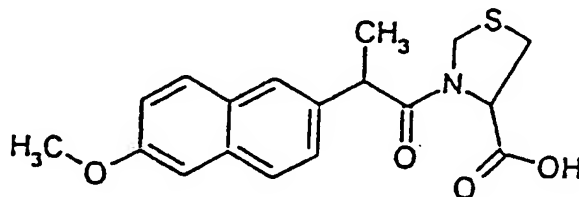
To a solution of 2-fluoro- $\alpha$ -methyl-(1,1'-biphenyl)-4-acetic acid (10 g, 41 mmols) in toluene (100 ml) and N,N-

dimethylformamide (10 ml) cooled at 0°C, oxalylchloride (3.52 ml, 82 mmoles) is added. After 2 hours at room temperature, the solution is evaporated at reduced pressure. The obtained residue is dissolved in acetone (50 ml) and the solution is added to a solution of 4-thiazolidinocarboxylic acid (5.44 g, 41 mmoles) and triethylamine (14.9 ml, 106 mmoles) in acetone (50 ml) cooled at 0°C. After 2 hours the mixture is acidified with HCl 4 N, concentrated under vacuum, the residue is treated with ethyl acetate and the organic phase is washed first with HCl 2 N, then with water. The organic phase is anhydriified with sodium sulphate and evaporated at reduced pressure. By crystallization with ethyl acetate/n-hexane, 9.4 ml of the expected product are obtained in the form of a white solid having m.p. 142°-147°C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 7.74-7.62 (4H, m), 7.35 (2H, t), 7.18-7.13 (2H, m), 5.06 (1H, m), 4.63 (1H, d), 4.42 (1H, d), 4.14 (1H, q), 3.13 (2H, m), 1.53 (3H, d).

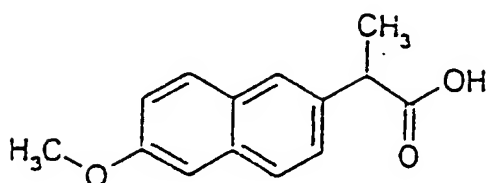
#### EXAMPLE 17

Synthesis of 3-(6-methoxy- $\alpha$ -metil-2-naphthalenacetyl) thiazolidin-4-carboxylic acid

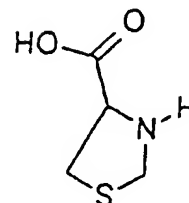


starting from naproxene of formula (VI). The precursor of B is

(L)-4-thiazolidin carboxylic acid (formula PIV)



(VI)



(PIV)

a) Synthesis of 3-(6-methoxy- $\alpha$ -methyl-2-naphthalenacetyl)thiazolidin-4-carboxylic acid

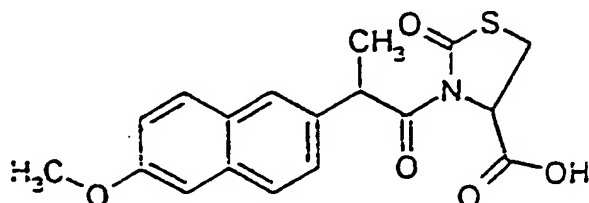
To a solution of 6-methoxy- $\alpha$ -methyl-2-naphthalenacetic acid (4.02 g, 17.5 mmol) in toluene (30 ml) and N,N-dimethylformamide (0.3 ml) cooled at 0°C, oxalylchloride (2.92 ml, 34.06 mmol) is added. After 2 hours at room temperature, the solution is evaporated at reduced pressure. The obtained residue is dissolved in acetone (50 ml) and the solution is added to a solution of 4-thiazolidinocarboxylic acid (2.33 g, 17.5 mmol) and triethylamine (6.34 ml, 45.5 mmol) in acetone (50 ml) cooled at 0°C. After 2 hours the mixture is acidified with HCl 4 N, concentrated under vacuum, the residue is treated with ethyl acetate and the organic phase is washed first with HCl 2 N, then with water. The organic phase is anhydriified with sodium sulphate and evaporated under reduced pressure. 4.43 g of the expected product are obtained in the form of a white solid having m.p. 165°-168°C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 7.75-7.66 (3H, m), 7.34 (1H, d), 7.14-7.11

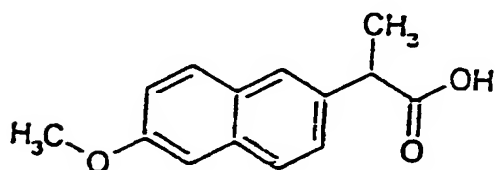
(2H, m), 5.14 (1H, m), 4.80-4.61 (2H, m), 4.07 (1H, q), 3.91 (3H, s), 3.30-3.23 (2H, m), 1.53 (3H, d).

### EXAMPLE 18

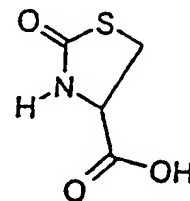
Synthesis of the 3-(6-methoxy- $\alpha$ -methyl-2-naphthalenacetyl)-(R)-2-oxothiazolidin-4-carboxylic acid



starting from naproxene of formula (VI). The precursor of B is (L)-2-oxo-4-thiazolidin carboxylic acid (formula PV)



(VI)



(PV)

a) synthesis of the 3-(6-methoxy- $\alpha$ -methyl-2-naphthalenacetyl)-(R)-2-oxothiazolidin-4-carboxylic acid

To a solution of 6-methoxy- $\alpha$ -methyl-2-naphthalenacetic acid (7.0 g, 30.4 mmol) in toluene (100 ml) and N,N-dimethylformamide (10 ml) cooled at 0°C, oxalylchloride (5.23 ml, 61 mmol) is added. After 2 hours at room temperature the solution is evaporated under reduced pressure. To the solution of the obtained residue dissolved in tetrahydrofuran (50 ml) a mixture formed of 2-oxothiazolidin-4-carboxylic acid (4.07 g.

27.6 mmol), 4-dimethylaminopyridine (0.84 g, 6.9 mmol), triethylamine (7.69 ml, 55.2 mmol) in tetrahydrofuran (50 ml) cooled at -10°C is added. It is left at room temperature for 24 hours. The reaction mixture is washed with HCl 5%, then with water. The organic phase is anhydri-fied with sodium sulphate and then evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with methylene chloride/methanol 95/5. 6.79 g of the expected product are obtained in the form of an amorphous solid.

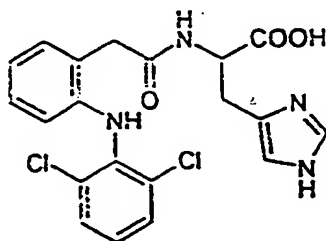
#### Elementary analysis

Calculated C: 60.16% H: 4.76% N: 3.89% S: 8.92%

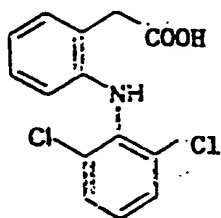
Found C: 60.22% H: 4.80% N: 3.83% S: 8.91%

#### EXAMPLE 19

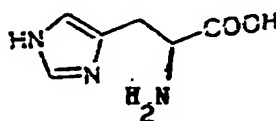
Synthesis of [2-[(2,6-dichlorophenyl)amino]benzeneacetyloxy]-  
-(L)-histidine



wherein the precursor drug of the invention compound is diclofenac of formula (XXIX) and the precursor compound of B is (L)-histidine of formula (PII):



(XXIX)



(PII)

a) synthesis of [2-[(2,6-dichlorophenyl)amino]benzeneacetyloxy]  
(L)-histidine

To a solution of diclofenac (3 g, 10.13 mmoles) in tetrahydrofuran (50 ml) cooled at 0°C, 1,1'-carbonyldiimidazole (1.69 g, 10.13 mmoles) is added under stirring. After 10 minutes the solution is treated with (L) histidine (1.57 g, 10.13 mmoles) and it is left under stirring at room temperature for 4 hours. The reaction mixture is concentrated under vacuum, treated with methylene chloride and then washed in sequence with HCl 1% and with water. The organic phase is anhydriified with sodium sulphate and evaporated under vacuum. The obtained residue is purified by chromatography on silica gel column, eluting with ethyl acetate. [2-[(2,6-dichlorophenyl)amino]benzeneacetyloxy] (L)-histidine is obtained. Yield: 61%

#### Elementary analysis

Calculated      C: 55.45%   H: 4.18%   N: 12.92%   Cl: 16.36%

Found            C: 55.48%   H: 4.23%   N: 12.88%   Cl: 16.25%

#### PHARMACOLOGICAL TESTS

##### EXAMPLE

##### Acute Toxicity

Acute toxicity has been evaluated by administering to a group of 10 rats weighing 20 g a single dose of each of the tested compounds, by cannula, by os in an aqueous suspension of carboxymethylcellulose 2% w/v.

The animals are kept under observation for 14 days. In no animal of the group toxic symptoms have appeared, even after administration of a 100 mg/Kg dose.

#### EXAMPLE F1

Test 1 - experimental model in vivo with N-ethylmaleimide (NEM): study of the gastric tolerability of some drugs screened as precursors of the compounds of the invention.

The animals (rats, weight about 200 g) are distributed in the following groups (No. 10 animals for group):

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when by parenteral route),

2° group: treatment: carrier + NEM,

B) Groups administered with each drug:

group I: treatment: carrier + drug,

group II: treatment: carrier + drug + NEM.

The drugs assayed in this experiment are the following (Table I): indomethacin, ambroxol, mesalamine, sodic alendronate, tacrine, omeprazol, misoprostol.

Indomethacin, ambroxol and alendronate are administered by os, mesalamine by intracolonic (rectal) route and tacrine, omeprazol, misoprostol by subcutaneous route.

The maximum tolerated dose, determined by administering



each substance by the above said routes to the animals not treated with NEM, is reported in Table I. With higher doses than those reported in the Table, enteropathy, diarrhoea, depression, tremor and sedation have appeared in the animals.

In this experimental model the animals are at first treated with NEM by subcutaneous injection at a dose of 25 mg/kg in physiologic solution. The drug is administered one hour later, in suspension in the carrier. Animals are sacrificed after 24 hours and evaluation of the damage to the gastrointestinal mucosa is made by counting the number of rats, inside each group, with lesions to the stomach at a visual inspection. The total number of said rats is then divided by the total number of rats of the group and multiplied by 100. The thus obtained percentages are reported in Table I. The Table shows that in the groups of rats treated with said drugs without NEM, no gastric lesions were detectable.

All the rats of group II (treated with NEM) showed gastric lesions after administration with the following drugs: indomethacin, ambroxol, mesalamine, sodic alendronate, tacrine. Said drugs therefore can be used in the synthesis of the products of the invention.

Omeprazol and misoprostol cannot instead be used, on the basis of the results provided in test 1, for preparing the products of the invention.

#### EXAMPLE F2

Test 2 (in vitro): inhibition of apoptosis (DNA fragmentation) induced in the endothelial cells by CIP in the presence of some drugs screened as precursors of the compounds of the invention.

The following precursor drugs (Table II): indomethacin, paracetamol, clopidogrel, salbutamol, ambroxol, sodic alendronate, dipylline, cetirizine, enalapril, nicotinamide, ampicilline, aciclovir, mesalamine, tacrine, simvastine, omeprazol have been tested.

Human endothelial cells of the umbilical vein are prepared according to a standard method. Fresh umbilical veins are filled with a collagenase solution 0.1% by weight and incubated at 37°C for 5 minutes.

Subsequently the veins are perfused with the medium M 199 (GIBCO, Grand Island, NY) pH 7.4 with 0.1% (weight/volume) of collagenase, added with 10% of bovine fetus serum (10 mcg/ml), sodium heparin (50 mcg/ml), thimidine (2.4 mcg/ml), glutamine (230 mcg/ml), penicillin (100 UI/ml), streptomycin (100 mcg/ml) and streptomycin B (0.125 mcg/ml). The cells are collected from the perfusate by centrifugation at 800 rpm and harvested in culture flasks T-75, pretreated with human fibronectin. Cells are then harvested in the same medium, added with bovine hypothalamic growth factor (100 ng/ml). When the cells of the primary cell culture (the cells directly removed from ex-vivo umbilical vein) form a single layer of confluent cells (about 8,000,000 cells/flask), harvesting is

stopped and the layers are washed and trypsinized. The cellular suspensions are transferred into wells of a culture plate having 24 wells, half of said wells being added with the same culture medium containing the drug at a  $10^{-4}$ M concentration, and harvested in a thermostat at 37°C at a constant moisture (90%),  $\text{CO}_2 = 5\%$ . When the drug is not soluble in the culture medium, it is formerly dissolved in a small amount of dimethylsulphoxide. The maximum amount of dimethylsulphoxide which can be added to the culture medium is 0.5%. Only the cells coming from these first subcultures are used for the tests with cumene hydroperoxide (CIP). The cells are identified as endothelial cells by morphological examination and by the specific immunological reaction towards factor VIII; these cultures did never show contaminations from myocytes or fibroblasts.

Before starting the test, the cellular culture medium is removed and the cellular layers are carefully washed with a standard physiologic solution buffered with phosphate 0.1 M pH 7.0, at the temperature of 37°C. The content of each well is then incubated for one hour with a CIP suspension in the culture medium at a 5 mM concentration. Evaluation of the cellular damage (apoptosis) is carried out by determining the per cent variation of the DNA fragmentation in the cultures containing the drug + CIP with respect to the controls treated with CIP only. Said % variation of DNA fragmentation is

determined by evaluating the fluorescence variation by a BX60 Olympus microscope (Olympus Co., Roma) set at the wave length of 405-450 nm, of the test samples with respect to the optical density of the controls. The fluorescence of each sample was determined on 5 replicates. Statistic evaluation has been made with t Student test ( $p < 0.01$ ).

Results are given in Table II and show that indomethacin, paracetamol, clopidogrel, salbutamol, sodic alendronate, dipylline, cetirizine, enalapril, nicotinamide, ampicilline, aciclovir, tacrine, omeprazol do not significantly inhibit apoptosis; these drugs can therefore be used for preparing the products of the invention.

On the contrary ambroxol, mesalamine and simvastatine inhibit apoptosis. Therefore on the basis of the results of test 2 these compounds could not be used for preparing the products of the invention.

#### EXAMPLE F3

Test 3 - experimental in vivo model with N<sup>w</sup>-nitro-L-arginine-methyl ester (L-NAME): gastric tolerability (gastrointestinal damage incidence), hepatic (GPT dosage, glutamic-pyruvic transaminase) and cardiovascular (blood pressure) tolerability of some drugs screened as precursors of the compounds of the invention.

The experimental model adopted is according to J. Clin. Investigation 90, 278-281, 1992.

The endothelial dysfunction is evaluated by determining the damage induced by L-NAME administration to the gastrointestinal mucosa, the hepatic damage (GPT increase), and the vascular endothelium or cardiovascular damage as blood hypertension.

The animals (rats, average weight 200 g) are divided in groups as herein below described. The group receiving L-NAME is treated for 4 weeks with said compound dissolved at the concentration of 400 mg/litre in drinking water. The following groups (No. 10 animals for group) are constituted:

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when by parenteral route),

2° group: treatment: carrier + L-NAME,

B) Groups treated with the drug:

3° group: treatment: carrier + drug,

4° group: treatment: carrier + drug + L-NAME.

The drugs used in the test are paracetamol, doxorubicin, simvastatine, omeprazol and misoprostol. Each drug is administered once a day for 4 weeks.

The maximum tolerated dose of the drug being administered to the animals is determined by evaluating, in a separate dose scaling up experiment on untreated animals, the appearance in

the animals of symptoms such as enteropathy, diarrhoea, depression, tremor, sedation.

At the end of the four weeks access to water is prevented and after 24 hours the animals are sacrificed.

One hour before the sacrifice blood pressure is determined and a blood pressure increase is taken as an indication of a damage being occurred to vascular endothelium.

The damage to the gastric mucosa is evaluated as previously mentioned in test 1 (ex. F1). The hepatic damage is determined by evaluation after the sacrifice of the glutamic-pyruvic transaminase (GPT increase).

The drug meets test 3 and it can therefore be used for preparing the compounds of the invention, when in the group of rats treated with L-NAME + drug + carrier, an higher hepatic damage (higher GPT values) and/or higher gastric damage and/or higher cardiovascular damage (higher blood pressure) are found in comparison with the group treated with the carrier only, or the group treated with carrier + drug, or the group treated with carrier + L-NAME.

The test results are reported in Table IV. The % gastric lesions have been determined as in Test 1. The % GPT and % blood pressure values are referred to the corresponding value found in the animals of the 1st group of the control groups. The average value of the blood pressure in this group was of  $105 \pm 8$  mmHg.

The results obtained show that paracetamol, doxorubicin and simvastatine cause hepatic damage and gastroenteropathy (GPT values and the gastric lesions are % higher compared both with the corresponding groups treated with the drug, in the absence of L-NAME, and with the controls treated with L-NAME).

These drugs can therefore be used for preparing the products of the invention.

Omeprazol and misoprostol should not instead be used, on the basis of this test, for preparing the products of the invention.

#### EXAMPLE F4

Test 4: inhibition of the radical production from DPPH of some substances used as precursors of B.

The method is based on a colorimetric test in which DPPH (2,2-diphenyl-1-picryl-hydrazyl) is used as the compound-forming radicals (M.S. Nenseter et Al., Atheroscler. Thromb. 15, 1338-1344, 1995).

Solutions in methanol of the tested substances at a final concentration 100  $\mu$ M are initially prepared. 0.1 ml of each of these solutions are added to aliquots of 1 ml of a methanol solution 0.1 M of DPPH and then the final volume is brought to 1.5 ml. After having stored the solutions at room temperature away from light for 30 minutes, the absorbance at the wave length of 517 nm is read. It is determined the absorbance decrease with respect to the absorbance of a solution

containing the same concentration of DPPH.

The efficacy of the test compound to inhibit the production of radicals, or antiradical activity, is expressed by the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein  $A_s$  and  $A_c$  are, respectively, the absorbance values of the solution containing the test compound together + DPPH and of the solution containing only DPPH.

The compound to be used according to the present invention meets test 4 if radical production inhibition, as above defined, is equal to or higher than 50%.

In Table V the results obtained with the following substances are reported: N-acetylcysteine, cysteine, ferulic acid, (L)-carnosine, gentisic acid, 4-thiazolidin carboxylic acid and 2-oxo-4-thiazolidin carboxylic acid.

Table V shows that:

- N-acetylcysteine, cysteine, ferulic acid, (L)-carnosine, gentisic acid meet test 4 since they inhibit the production of radicals induced by DPPH to an extent higher than 50%.
- The 4-thiazolidin carboxylic acid and the 2-oxo-4-thiazolidin carboxylic acid are ineffective, since they do not inhibit radical production from DPPH. Therefore they can be used as precursors of the compound B in the synthesis of the compounds according to the present



invention, if they meet test 5.

EXAMPLE F5

Test 5: inhibition of the radical production from  $\text{Fe}^{\text{II}}$  from compounds used as precursors of B

0.1 ml aliquots of  $10^{-4}$  M methanolic solutions of 4-thiazolidin carboxylic acid and 2-oxo-4-thiazolidin carboxylic acid are added to test tubes containing an aqueous solution formed by mixing 0.2 ml of 2 mM deoxyribose, 0.4 ml of buffer phosphate pH 7.4 100 mM and 0.1 ml of 1 mM  $\text{Fe}^{\text{II}}(\text{NH}_4)_2(\text{SO}_4)_2$  in 2mM HCl. The test tubes are then kept at a temperature of 37°C for one hour. Then in each test tube are added in the order 0.5 ml of a 2.8% solution in trichloroacetic acid in water and 0.5 ml of an aqueous solution 0.1 M thio barbituric acid. A reference blank is constituted by substituting the above 0.1 ml aliquots of the test compound methanolic solutions with 0.1 ml of methanol. The test tubes are closed and heated in an oil bath at 100°C for 15 minutes. A pink coloration develops the intensity of which is proportional to the quantity of deoxyribose undergone to radical oxidative degradation. The solutions are cooled at room temperature and their absorbances at 532 nm are read against the blank.

The inhibition induced by the precursor of B or  $\text{B}_1$  or C = -T<sub>C</sub>-Y-H (wherein the free valence is saturated as above defined) in the confront of radical production from  $\text{Fe}^{\text{II}}$  is determined as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein  $A_s$  and  $A_c$  are respectively the absorbance values of the solution containing the tested compound + the iron salt and that of the solution containing only the iron salt.

The results are reported in the attached Table, which shows that both acids are active in inhibiting the radical production from the iron ion. Therefore these compounds can be used as precursors of B for obtaining the present invention compounds.

#### EXAMPLE F6

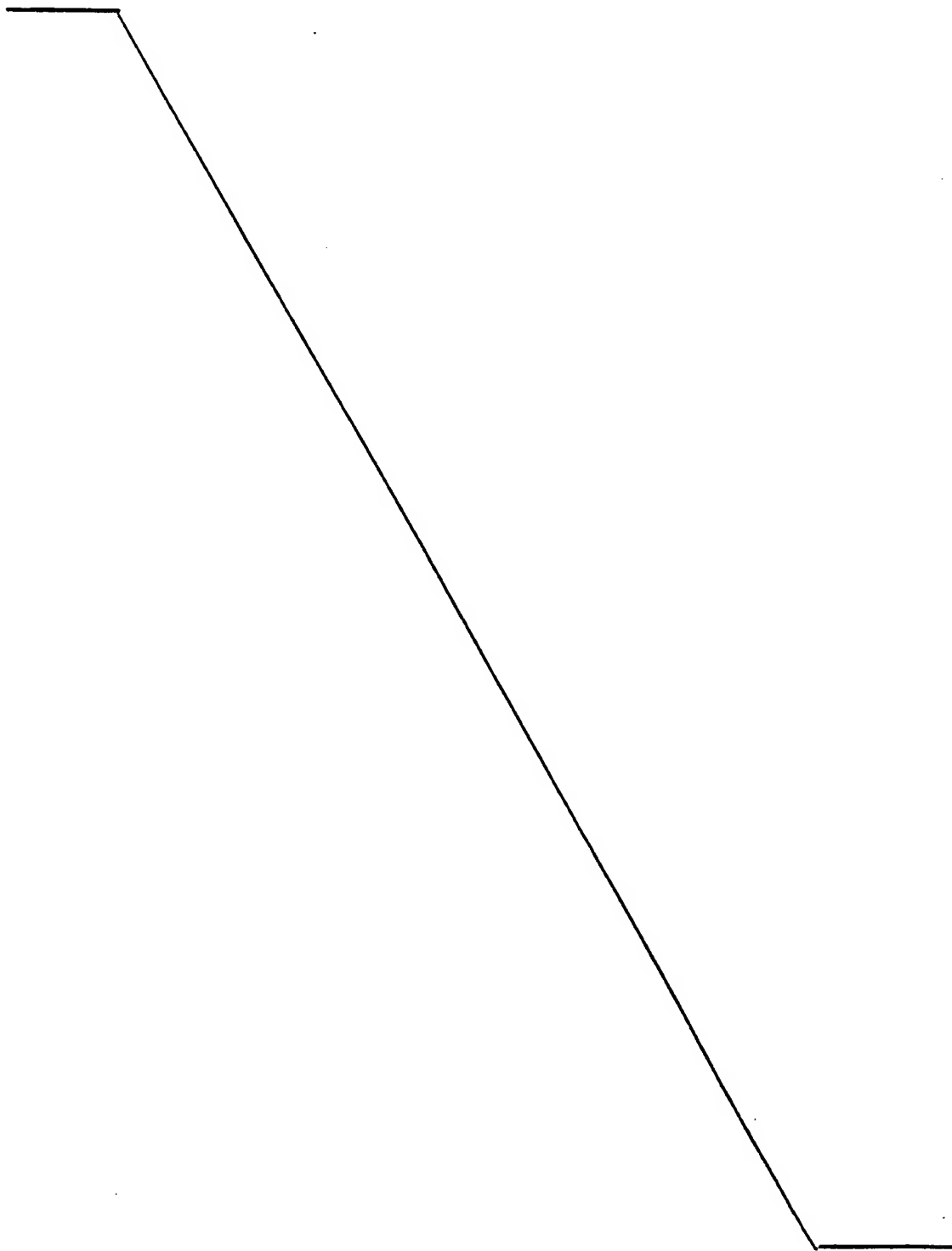
Gastric tolerability test of the compounds according to the invention with respect to the corresponding precursor drugs in conditions of endothelial trouble induced by L-NAME ( $N^W$ -nitro-L-arginine-methyl ester).

Example F3 was repeated and it was evaluated gastric tolerability both of the following precursor drugs and of the corresponding derivatives according to the present invention:

- Diclofenac and corresponding derivative according to Ex. 15,
- Piroxicam and corresponding derivative according to Ex. 14.
- Aspirin and corresponding derivative according to Ex. 13.

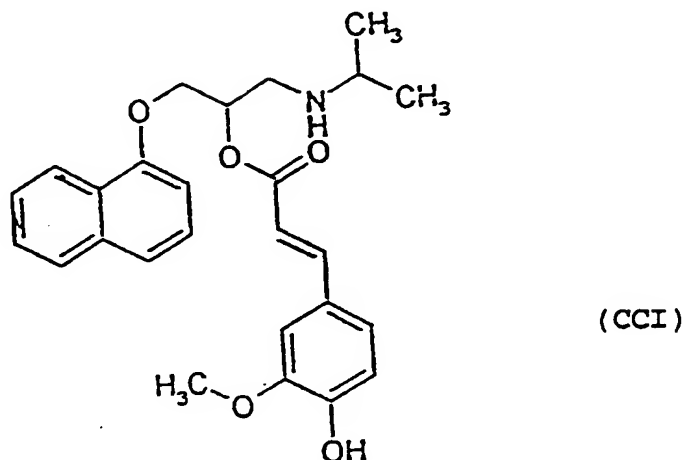
The results are reported in Table VI and show that, by administering at the same dose the compounds of the invention and the corresponding precursor drug, gastropathy incidence

results remarkably reduced or disappeared in the groups treated with the compounds of the invention.

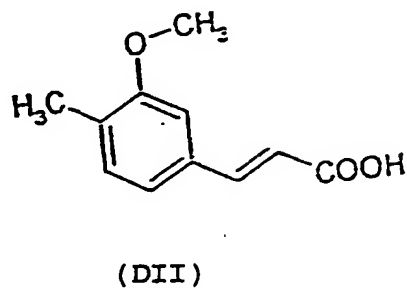
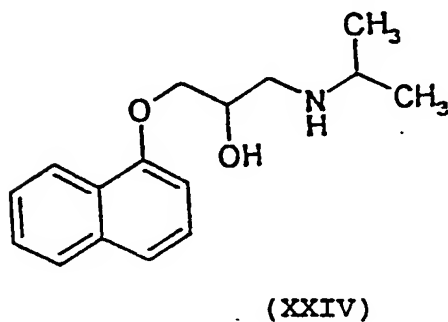


EXAMPLE 20

Synthesis of 3(3-methoxy-4-hydroxy-phenyl)-2-trans propenoic acid 1-[(1-methylethyl)amino]-3-(1-naphtalenoxy)-2-propyl ester of formula (CCI)



starting from propranolol of formula (XXIV). The precursor of B is ferulic acid (formula DII)



Compound (CCI) has been obtained according to the process of Example 8. Yield: 30%

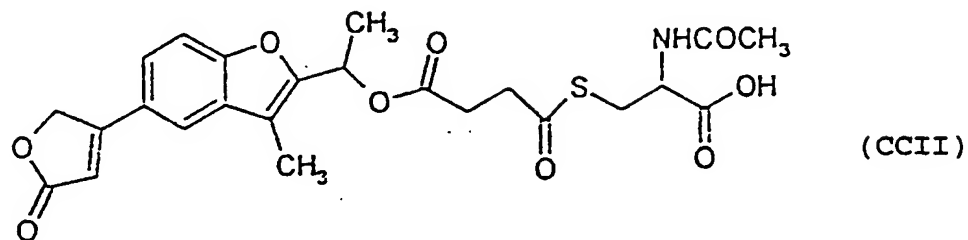
## Elemental analysis

Calculated :	C : 71.71	H : 6.71	N : 3.22
Found:	C : 71.79	H : 6.75	N : 3.17

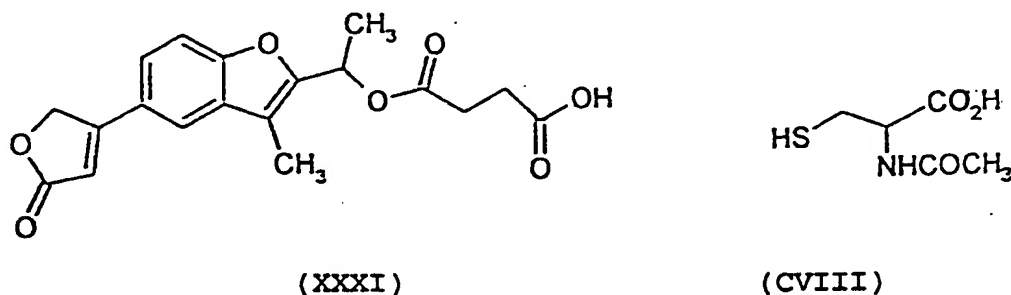
EXAMPLE 21

Synthesis of N-acetyl-S-[1-[5-(2,5-dihydro-5-oxo-3-furanyl)-3-

methyl-2-benzofuranyl]ethyloxy-4-oxo-butanoyl]-cysteine of formula (CCII)



starting from benfurodil hemisuccinate of formula (XXXI). The precursor of B is N-acetylcysteine of (formula CVIII)



Compound (CCII) has been obtained according to the process of Example 1. Yield: 13%

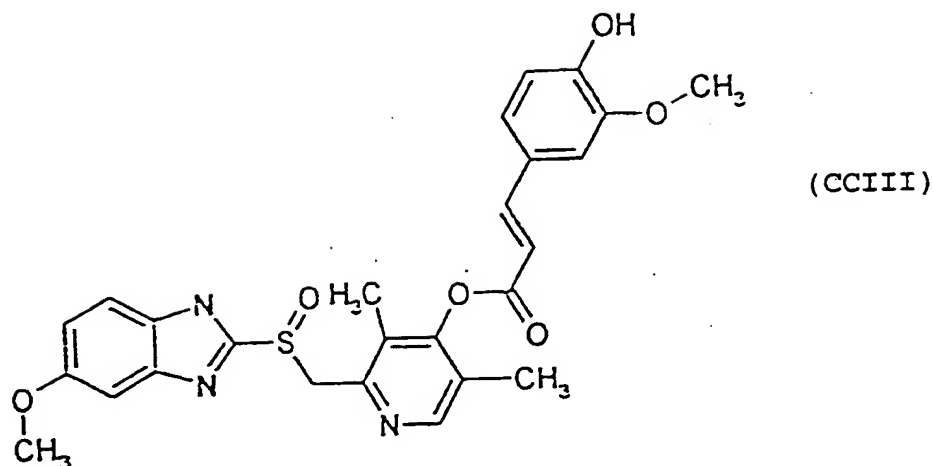
#### Elemental analysis

Calculated : C : 57.25 H : 5.00 N : 2.78 S : 6.37

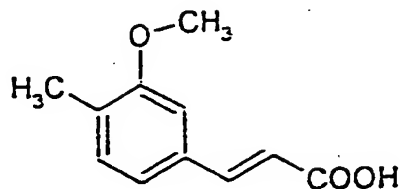
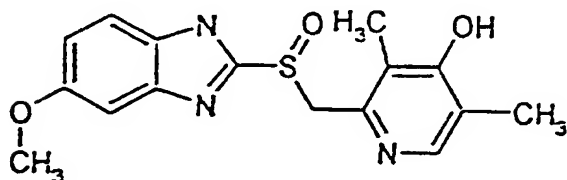
Found: C : 57.30 H : 5.02 N : 2,72 S : 6.35

#### EXAMPLE 22

Synthesis of 5-methoxy-2-[[[(3-methoxy-4-hydroxy-phenyl)-2-trans propenoyl oxy]-3,5-dimethyl-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole of formula (CCIII)



starting from 4-hydroxyomeprazole of formula (XXII) and ferulic acid (formula DII)



Compound (CCIII) has been obtained according to the process of Example 8. Yield: 43%

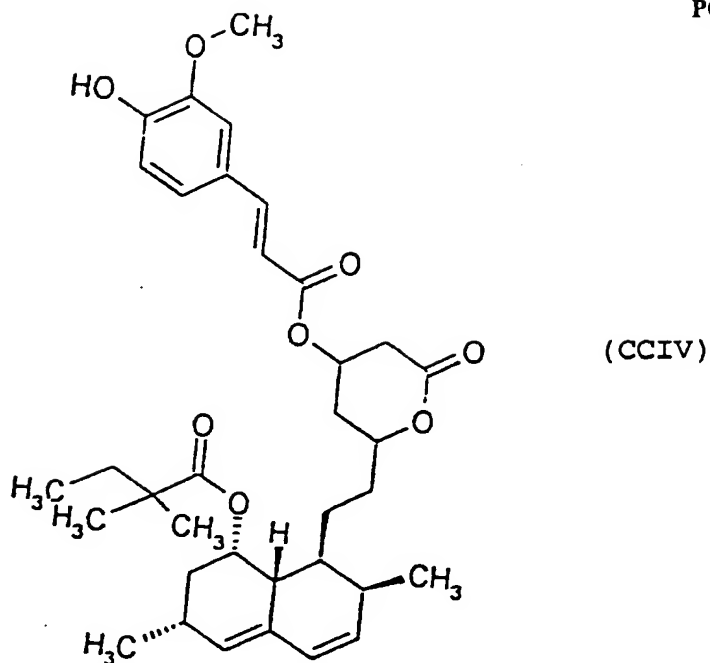
Elemental analysis

Calculated : C : 61.65 H : 4.78 N : 8.30 S : 6.33

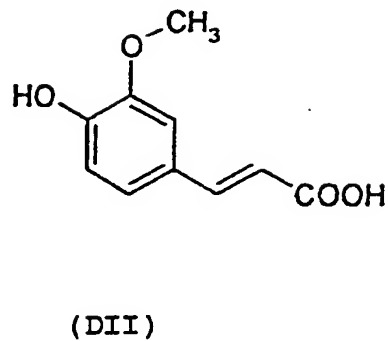
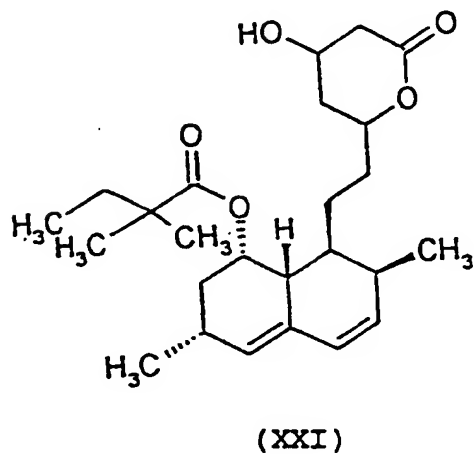
Found: C : 61.71 H : 4.85 N : 8.25 S : 6.35

#### EXAMPLE 23

Synthesis of [1S-[1 $\alpha$ ,3 $\alpha$ ,7 $\beta$ ,8 $\beta$ , (2S\*,4S\*)]]-2,2-dimethylbutanoic acid 1,2,3,7,8,8-hexahydro-3,7-dimethyl-8-[2-[tetrahydro-4-[(3-methoxy-4-hydroxy-phenyl)-2-trans propenoyloxy]-6-oxo-2H-piran-2-yl]ethyl]-1-naphthalenyl ester of formula (CCIV)



starting from simvastatine of formula (XXI) and ferulic acid of formula (DII)



Compound (CCIV) has been obtained according to the process of Example 8. Yield: 21%

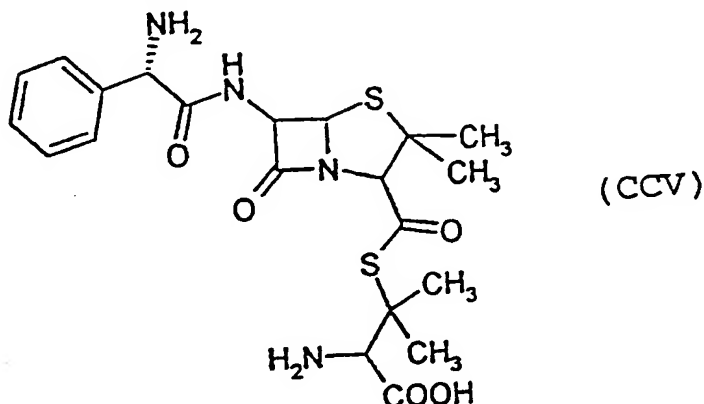
#### Elemental analysis

Calculated :            C : 70.68            H : 7.80

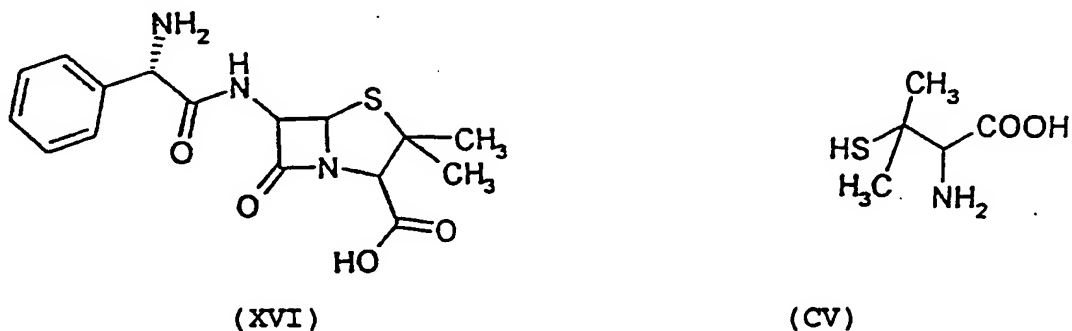
Found:                C : 70.70            H : 7.82

EXAMPLE 24

Synthesis of S-[4-D- $\alpha$ -aminobenzylpenicillaminoyl]penicillamine of formula (CCV)



starting from ampicillin of formula (XVI) and penicillamine of formula (CV)



Compound (CCV) is synthesized according to the process of Example 9. Yield: 13%

## Elemental analysis

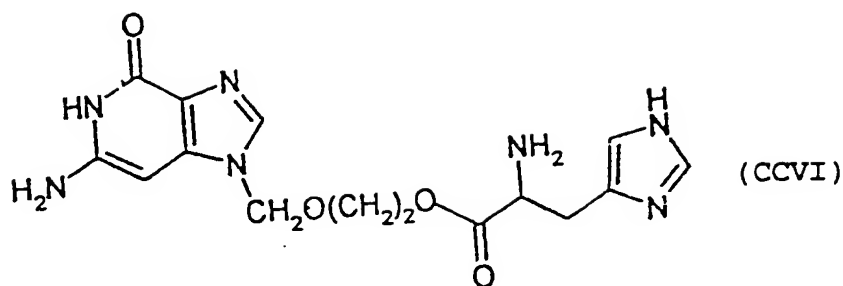
Calculated : C : 52.48 H : 5.87 N : 11.66 S : 13.34

Found: C : 52.51 H : 5.90 N : 11.61 S : 13.30

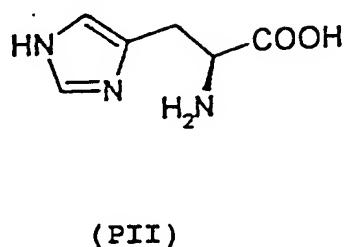
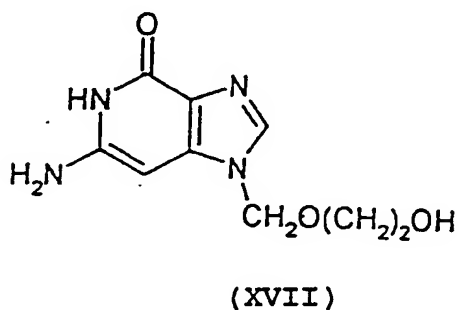
EXAMPLE 25

Synthesis of 9-[[2-[(S)- $\alpha$ -amino-1H-imidazole-4-propanoyl-oxy]ethoxy]-methyl]guanine of formula (CCVI)





starting from acyclovir of formula (XVII) and histidine of formula (PII)



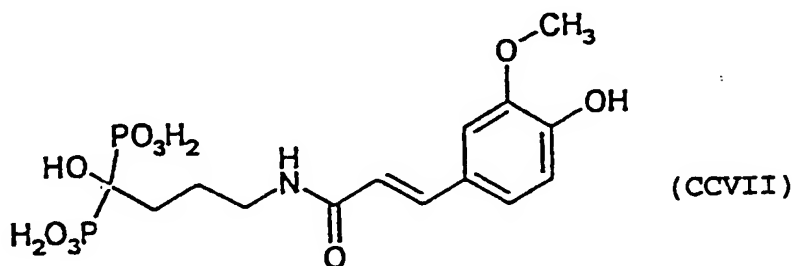
Compound (CCVI) has been obtained following the procedure of Example 19. Yield : 17%

Elemental analysis

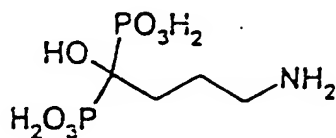
Calculated :	C : 50.14	H : 4.77	N : 27.29
Found:	C : 50.17	H : 4.75	N : 27.22

#### EXAMPLE 26

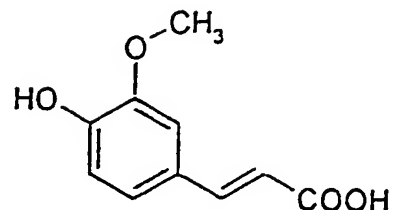
Synthesis of [4-amino-[(3-methoxy-4-hydroxy-phenyl)-2-trans propenoyl]-1-hydroxybutyliden] biphosphonic acid of formula (CCVII)



starting from alendronic acid of formula (XXXVI) and ferulic acid of formula (DII)



(XXXVI)



(DII)

Compound (CCVII) has been obtained following the procedure of Example 8. Yield : 10%

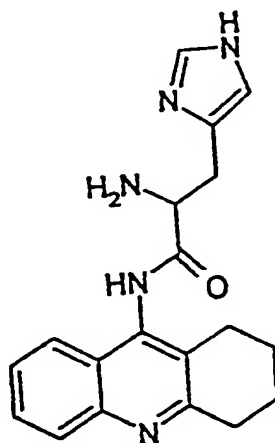
Elemental analysis

Calculated : C : 39.54 H : 4.98 N : 3.29 P : 14.57

Found: C : 39.57 H : 5.01 N : 3.24 P : 14.56

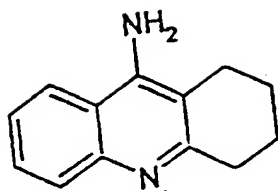
#### EXAMPLE 27

Synthesis of 5-[[[(S)- $\alpha$ -amino-1H-imidazole-4-propanoyl]amino]-1,2,3,4-tetrahydroacridine of formula (CCVIII)

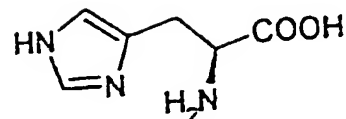


(CCVIII)

starting from tacrine of formula (XXXV) and histidine of formula (PII)



(XXXV)



(PII)

Compound (CCVIII) has been obtained according to the procedure of Example 19. Yield 15%

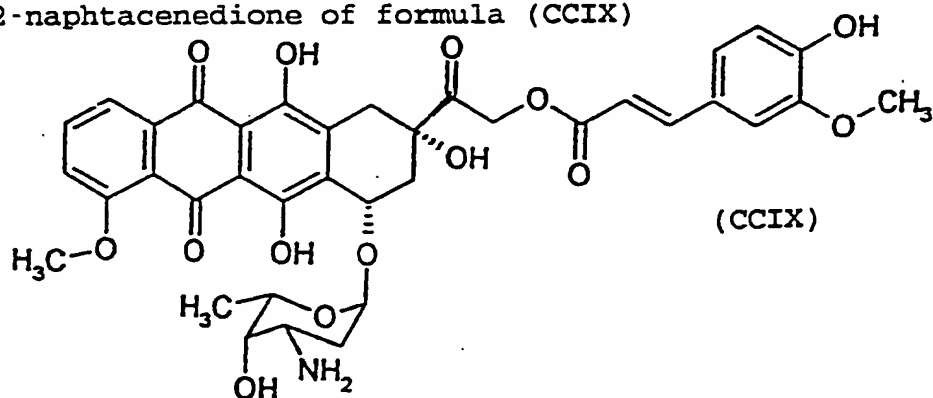
#### Elemental analysis

Calculated :            C : 68.04            H : 6.31            N : 20.88

Found:                C : 68.08            H : 6.37            N : 20.84

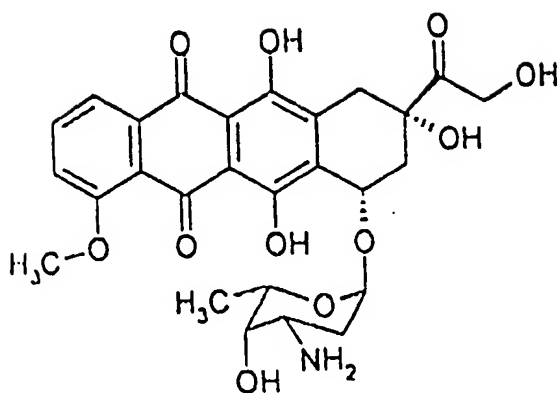
#### EXAMPLE 28

Synthesis of (8S-cis)-10[(3-amino,2,3,6-tri-deoxy- $\alpha$ -L-lyxo-exo pyranosyl)oxy]-7,8,9,10-tetrahydro,6,8,11-trihydroxy-8-[[[(3-methoxy-4-hydroxy-phenyl)-2-trans propenoyl-oxy-]methyl-oxo]-1-methoxy-5,12-naphtacenedione of formula (CCIX)

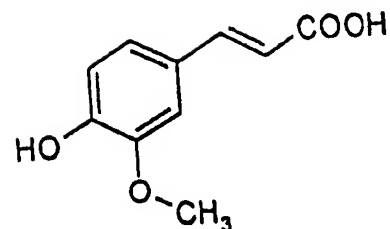


(CCIX)

starting from doxorubicin of formula (XXXII) and ferulic acid of formula (DII)



(XXXII)



(DII)

Compound (CCIX) has been obtained according to the procedure of

Example 8. Yield 10%

Elemental analysis

Calculated :	C : 61.75	H : 5.18	N : 1.95
--------------	-----------	----------	----------

Found:	C : 61.81	H : 5.22	N : 1.90
--------	-----------	----------	----------

#### EXAMPLE F7

Example F1 was repeated with three groups of rats (each group of of ten animals), all of them receiving NEM, and orally administered as it follows :

- a. control group : the vehicle formed of an aqueous suspension 1% w/v of carboxymethylcellulose,
- b. one group (group b - comparative ) administered at the same time with 100 mg/Kg (0.48 mmol/Kg) of ibuprofen + 79 mg/Kg (0.48 mmol/Kg) of N-acetylcysteine in the same above vehicle,
- c. one group (group c) administered with 170.4 mg/Kg (0.48 mmol/Kg) of the ester between indomethacin and N-acetyl cisteine (ref. ex. 2), in the above same vehicle.

The results are reported in Table VII and show that the mixture administered to group b (comparative) is less effective than the compound of the invention administered to group c in reducing gastric lesions.

Table I

Test 1 : Gastric tolerability of drugs representative of the drug classes illustrated in the present invention in animals not treated or treated with NEM (oxidative stress conditions). The % incidence is calculated from the ratio between the number of animals found with gastric lesions and that total of the group.			
Compound	dose (mg/Kg) /admin. route	Gastro-enteropathy (% incidence)	
		without NEM	with NEM
carrier		0	0
Indomethacin	7.5/p.o.	0	100
Ambroxol	25/p.o.	0	80
Mesalamine	750/i.c.	0	60
Alendronate	15/p.o.	0	90
Tacrine	1/s.c.	0	100
Omeprazol	30/s.c.	0	0
Misoprostol	0.5/s.c.	0	0

p.o. = per os; i.c. = by intracolonic route;  
s.c. = by subcutaneous route.

Table II

Test 2 : Inhibition of apoptosis (DNA fragmentation) induced by CIP in the endothelial cells in the presence of compounds representative of the drug classes illustrated in the present invention.	
Compound	Apoptosis % with respect to the controls treated only with CIP
Indomethacin	95
Paracetamol	120
Clopidogrel	110
Salbutamol	90
Ambroxol	70
Alendronate	160
Diphylline	95
Cetirizine	115
Enalapril	80
Nicotinamide	98
Ampicilline	94
Aciclovir	95
Mesalamine	74
Tacrine	90
Simvastatine	72
Omeprazol	90

Table III

Test 5 : Screening of the effectiveness of the listed substances to inhibit radical production induced by Fe <sup>II</sup>	
Compound	% Radical Inhibition from Fe <sup>II</sup>
Blank	0
2-oxo-4-thiazolidin carboxylic acid	100
4-thiazolidin carboxylic acid	100
histidine	90

Table IV

Test 3 : Gastric tolerability (gastrointestinal damage incidence), hepatic (GPT, glutamic-pyruvic transaminase dosage), and cardiovascular (blood pressure) of some compounds representative of the drug classes illustrated in the present invention under conditions of endothelial trouble induced by L-NAME. The results relating to the blood pressure and GPT are expressed as % values compared with those found in animals treated with the only carrier, without L-NAME.						
Compound	dose mg/Kg /administ. route	Blood pressure %		GPT %		Gastroenteropathy %
		without L-NAME	with L-NAME	without L-NAME	with L-NAME	
Carrier		100	152	100	155	0
Paracetamol	300/i.p.	108	155	180	500	20
Doxorubicin	1/i.p.	120	145	195	360	30
Simvastatine	50/p.o.	85	148	122	220	0
Omeprazol	30/s.c.	100	150	100	160	0
Misoprostol	0.5/s.c.	100	142	100	160	0
						30
						90
						100
						60
						10
						5



Table V

Test 4: Screening of the effectiveness of the listed compounds in inhibiting radical production from DPPH	
Compound	% inhibition radical production from DPPH
Solvent	0
N-acetylcysteine	100
Cysteine	100
Ferulic acid	100
(L)-carnosine	80
Gentisic acid	80
4-thiazolidincarboxylic acid	0
2-oxo-4-thiazolidin carboxylic acid	0
histidine	0

Table VI

Gastric tolerability of derivatives according to the present invention in comparison with that of the corresponding precursor drugs		
Treatment	dose mg/Kg	Gastropathy & incidence
Carrier	-	30
diclofenac	10	100
diclofenac der. (Ex. 15)	10	10
piroxicam	10	100
piroxicam der. (Ex. 14)	10	0
aspirin	50	100
aspirin der. (Ex. 13)	50	0

Table VII

Test on gastric tolerability following oral administration of NEM (Ex. F7)		
groups	dose mg/Kg p.o.	Gastropathy % incidence
controls	-	-
group b - comparative mixture ibuprofen (A) + N-acetylcysteine (B)	100(A)+79(B)	60
group c ester of ibuprofen with N-acetylcysteine	170.4	10

## CLAIMS

1. Compounds or their salts of general formulas (I):



wherein:

$A = R-T_1-$ , wherein

R is the drug radical and

$T_1 = (CO)_t$  or  $(X)_{t'}$ , wherein  $X = O, S, NR_{1C}$ ,  $R_{1C}$  is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, or a free valence, t and t' are integers and equal to zero or 1, with the proviso that  $t = 1$  when  $t' = 0$ ;  $t = 0$  when  $t' = 1$ ;

$B = -T_B-X_2$  wherein

$T_B = (CO)$  when  $t = 0$ ,  $T_B = X$  when  $t' = 0$ , X being as above defined;

$X_2$ , monovalent radical, is such that the corresponding precursor of B meets test 5 and/or test 4; said precursor of formula  $-T_B-X_2$ , wherein the  $T_B$  free valence is saturated with  $-OZ$  or  $Z$  wherein  $Z = H$  or  $R_{1a}$ , being  $R_{1a}$   $C_1-C_{10}$  = linear or when possible branched alkyl, preferably  $C_1-C_5$ ,

or with  $-Z^I-N-Z^{II}$ ,  $Z^I$  and  $Z^{II}$  being equal or

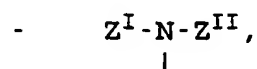
different and having the Z values, depending on whether  $T_B = CO$  or  $X$ , in connection with the t, t' values;

with the proviso that:

- the drug  $A = R-T_1-$ , wherein the free valence is saturated as hereinafter mentioned:

- when  $t' = 0$  with:

- $O-Z$  wherein  $Z = H$  or  $R_{1a}$ , or with



- when  $t = 0$  with  $X-Z$ , wherein  $X$  and  $Z$  as above defined,

is such as to meet at least one of tests 1-3;

wherein test 1 (NEM) is a test in vivo carried out on four groups of rats (each formed by 10 rats), the controls (two groups) and the treated (two groups) of which one group of the controls and one group of the treated respectively are administered with one dose of 25 mg/kg s.c. of N-ethylmaleimide (NEM), the controls being treated with the carrier and the treated groups with the carrier + the drug of formula  $A = R-T_1-$  wherein the free valence is saturated as above indicated, administering the drug at a dose equivalent to the maximum one tolerated by the rats that did not receive NEM, i.e. the highest dose administrable to the animal at which there is no manifest toxicity, i.e. such as to be symptomatologically observable; the drug complies with test 1, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when the

group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in the group treated with NEM + carrier + drug are observed gastrointestinal damages greater than those of the group treated with the carrier, or of the group treated with the carrier + drug, or of the group treated with the carrier + NEM;

- wherein test 2 (CIP) is a test in vitro wherein human endothelial cells from the umbilical vein are harvested under standard conditions, then divided into two groups (each group replicated five times), of which one is treated with a mixture of the drug  $10^{-4}$  M concentration in the culture medium, the other group with the carrier; then cumene hydroperoxide (CIP) having a 5 mM concentration in the culture medium is added to each of the two groups; the drug meets test 2, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), if a statistically significant inhibition of the apoptosis (cellular damage) induced by CIP is not obtained with  $p < 0.01$  with respect to the group treated with the carrier and CIP;

wherein test 3 (L-NAME) is a test in vivo carried out on four groups of rats (each group formed by 10 rats) for 4 weeks and receiving drinking water,

the controls (two groups) and the treated (two groups), of which one group of the controls and of the treated respectively receives in the above 4 weeks drinking water added of N- $\omega$ -nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/litre, the controls in the 4 weeks being administered with the carrier and the treated in the 4 weeks with the carrier + the drug, administering the carrier or the drug + carrier once a day, the drug being administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME, i.e., the highest dose administrable to animals at which no manifest toxicity appears, i.e. such as to be symptomatologically observable; after the said 4 weeks, the water supply is stopped for 24 hours and then sacrificed, determining the blood pressure 1 hour before sacrifice, and after sacrifice of the rats determining the plasma glutamic pyruvic transaminase (GPT) after sacrifice, and examining the gastric tissue; the drug meets test 3, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when in the group of rats treated with L-NAME + carrier + drug, greater hepatic damages (determined as higher values of GPT) and/or gastric and/or cardiovascular damages (determined as higher

values of blood-pressure) are found in comparison respectively with the group treated with the carrier alone, or with the group treated with the carrier + drug, or with the group treated with the carrier + L-NAME;

wherein test 4 is an analytical determination carried out by adding portions of methanol solutions of the precursor of B or B<sub>1</sub> at a 10<sup>-4</sup> M concentration, to a methanol solution of DPPH (2,2-diphenyl-1-picryl hydrazyl - free radical); after having maintained the solution at room temperature away from light for 30 minutes, it is read the absorbance at the wave length of 517 nm of the test solution and of a solution containing only DPPH in the same amount as in the test solution; and then the inhibition induced by the precursor towards the radical production by DPPH is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

wherein A<sub>s</sub> and A<sub>c</sub> are respectively the absorbance values of the solution containing the test compound + DPPH and that of the solution containing only DPPH; test 4 is met by the compounds used as precursors of B if the % inhibition as above defined is higher than or equal to 50%;



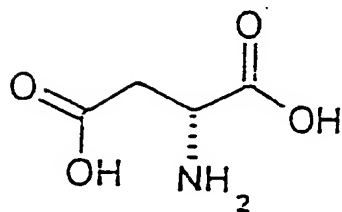
wherein test 5 is an analytical determination carried out by adding aliquots of  $10^{-4}$  M methanol solutions of the precursors of B to a solution formed by admixing a 2 mM solution of desoxyribose in water with 100 mM of phosphate buffer and 1 mM of the salt  $\text{Fe}^{\text{II}}(\text{NH}_4)_2(\text{SO}_4)_2$ ; after having thermostatted the solution at 37°C for one hour, are added, in the order, aliquots of aqueous solutions of trichloroacetic acid 2.8% and of thiobarbituric acid 0.5 M, heating is effected at 100°C for 15 minutes and the absorbance of the tested solutions is then read at 532 nm; the inhibition induced by the precursors of B in the confront of radical production by  $\text{Fe}^{\text{II}}$  is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c) \times 100$$

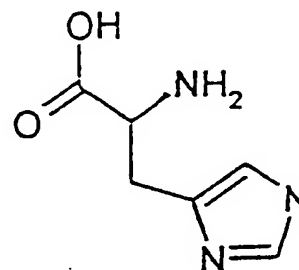
wherein  $A_s$  and  $A_c$  are respectively the absorbance values of the solution containing the tested compound and the iron salt and that of the solution containing only the iron salt; the compound meets test 5 when the % inhibition as above defined of the precursor of B is higher than or equal to 50%.

2. Compounds according to claim 1 wherein the precursor compound of B that meets test 5 is selected from the following compounds:

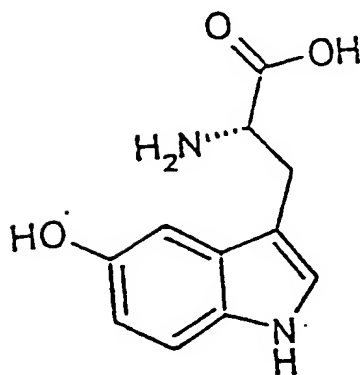
- Aminoacids: aspartic acid (PI), histidine (PII), 5-hydroxytryptophan (PIII), 4-thiazolidincaroxylic acid (PIV), 2-oxo-4-thiazolidincaroxylic acid (PV)



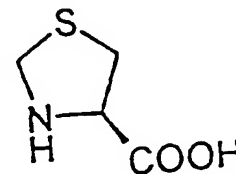
(PI)



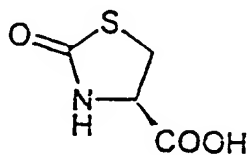
(PII)



(PIII)



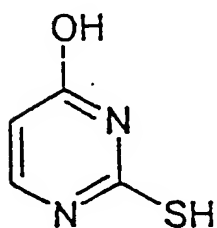
(PIV)



(PV)

- mono and polyalcohols or thiols: 2-thiouracil (QI), 2-mercaptoethanol (QII), esperidine (QIII), secalciferol (QIV), 1- $\alpha$ -OH vitamin D<sub>2</sub> (QV), flocalcitriol (QVI), 22-oxacalcitriol (QVII), the

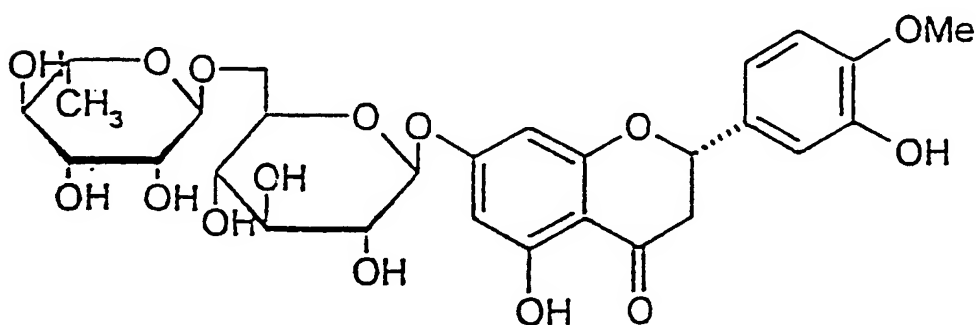
vitamin D3 derivative esterified with the vitamin A radical (QVIII), the formula (QIX) compound, 24,28-methylene-1 $\alpha$ -hydroxyvitamin D2 (QX) the compound derived from 1 $\alpha$ ,25-dihydroxyvitamin D2 (QXI), 2-mercaptoimidazol (QXII)



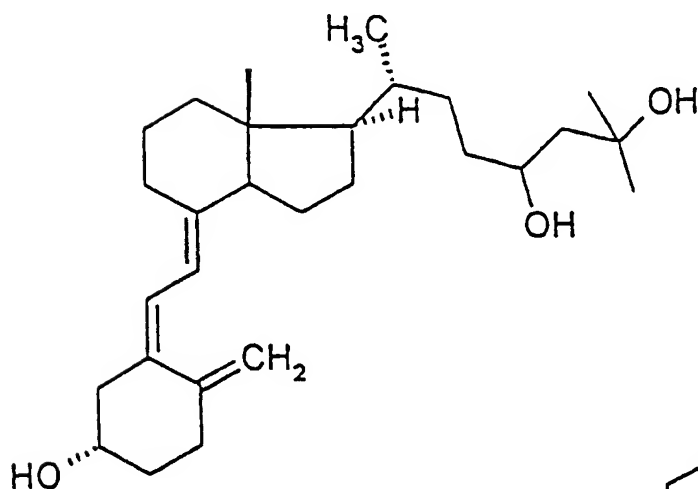
(QI)



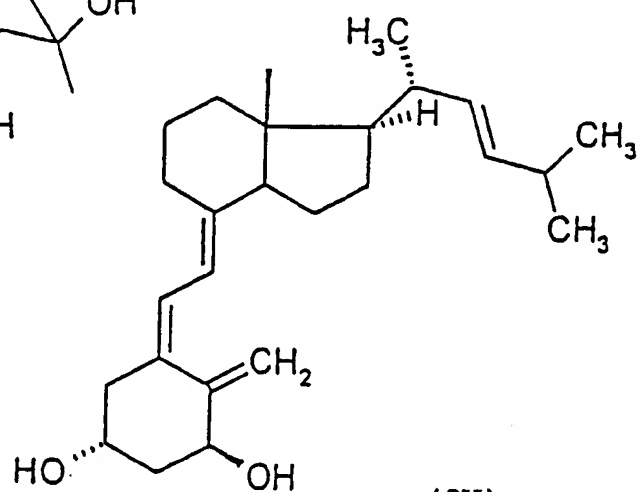
(QII)



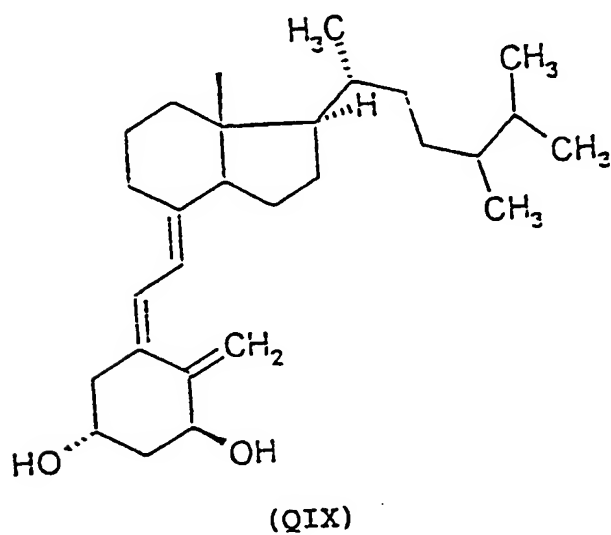
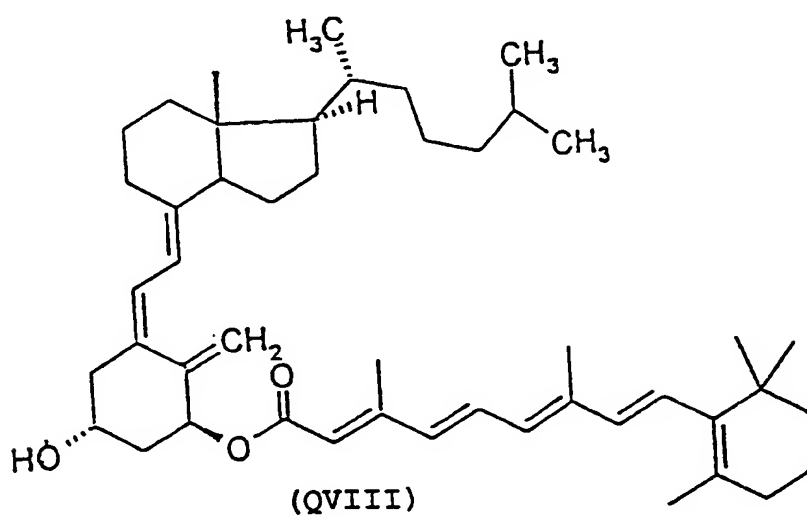
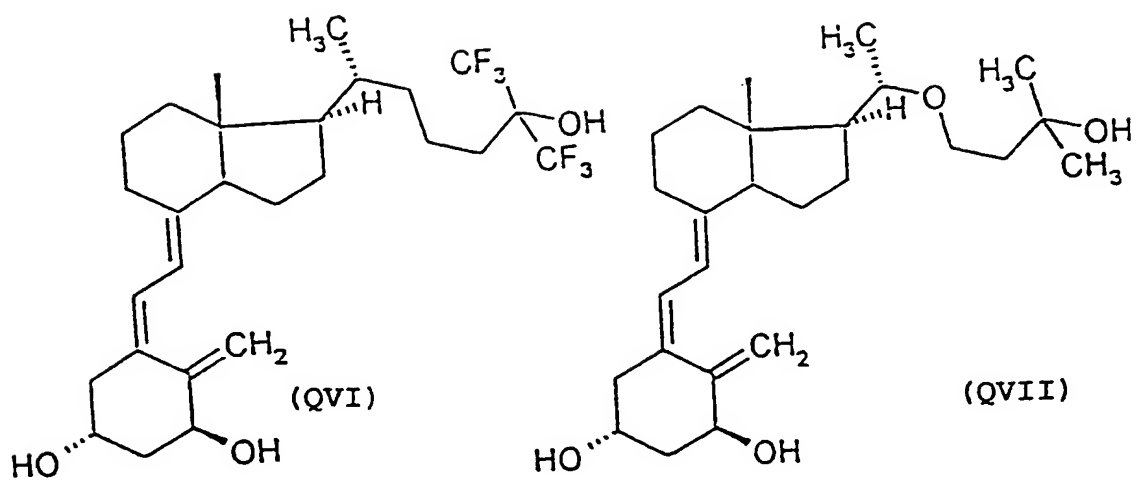
(QIII)

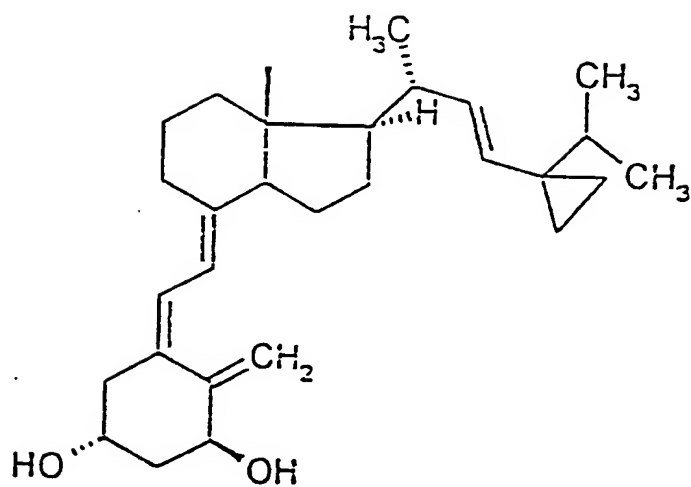


(QIV)

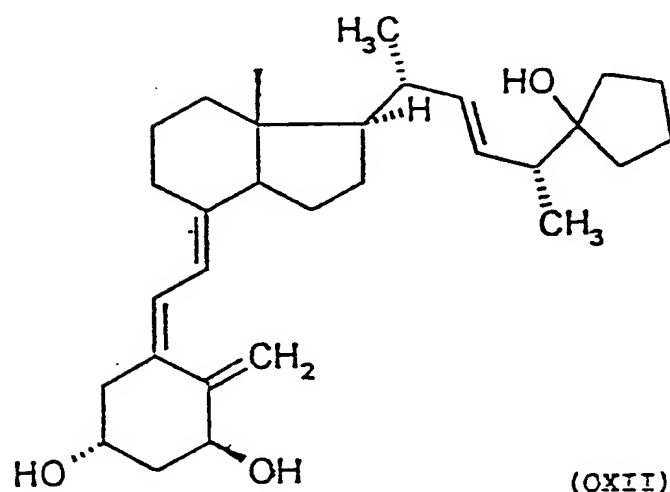


(QV)





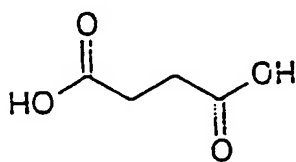
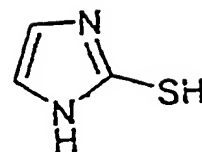
(QX)



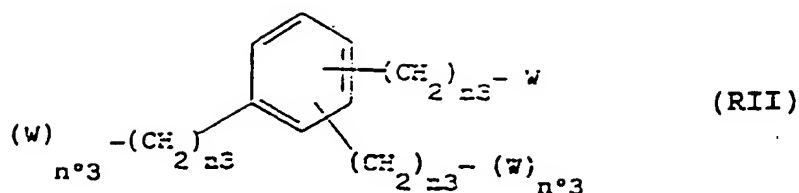
(QXI)

- succinic acid (RI)

(QXII)



(RI)

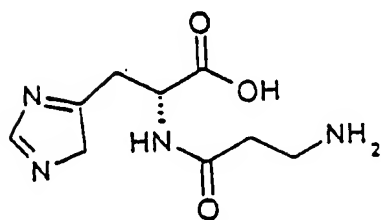


wherein  $n^{\circ}3$ , equal to or different from each other, are an integer equal to zero or one;  $n3$ , equal to or different from each other, are integers from zero to three;  $W$ , equal to or different from each other, are selected among the following:  $HX$  with  $X$  as above defined,  $COOH$ ,  $R'$ ,  $OR'$  wherein  $R'$  is a linear or when possible branched alkyl having from 1 to 20 carbon atoms, preferably from 1 to 6 carbon atoms;  $R_f$ ,  $OR_f$  wherein  $R_f$  is as  $R'$  but containing at least one halogen atom instead of  $H$ , preferably  $F$ ; at least one of the  $W$  radicals is  $XH$ , when the drug reactive function is a carboxyl; or  $COOH$  when the drug reactive function is  $XH$ ;

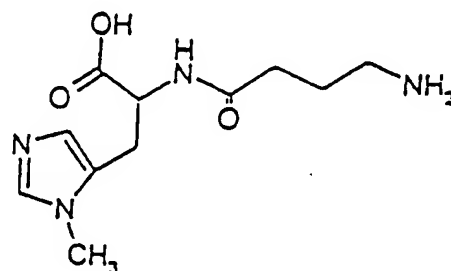
when  $n^{\circ}3 = 0$  if  $n3$  is different from zero then the free valence of the  $n3$  group is saturated with one of the following substituents:  $R'$ ,  $OR'$ ,  $R_f$ ,  $OR_f$ ,  $H$ , when  $n^{\circ}3 = 0$  and  $n3 = 0$ , the free valence is saturated with  $H$ .

3. Compounds according to claim 1, wherein the precursor compound of B which meets test 4 is selected from the following classes of compounds:

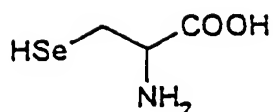
- Aminoacids, selected from the following: L-carnosine (formula CI), anserine (CII), selenocysteine (CIII), selenomethionine (CIV), penicillamine (CV), N-acetylpenicillamine (CVI), cysteine (CVII), N-acetylcysteine (CVIII), glutathione (CIX) or its esters, preferably ethyl or isopropyl ester:



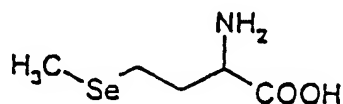
(CI)



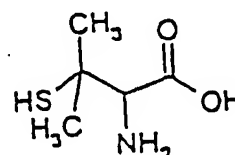
(CII)



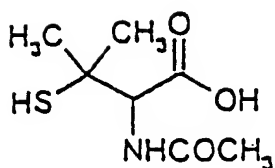
(CIII)



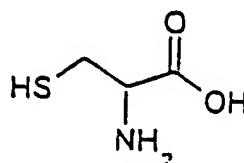
(CIV)



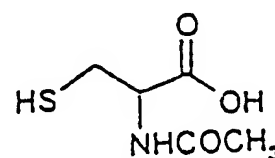
(CV)



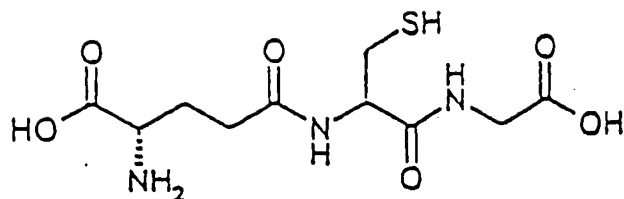
(CVI)



(CVII)



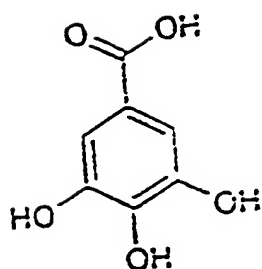
(CVIII)



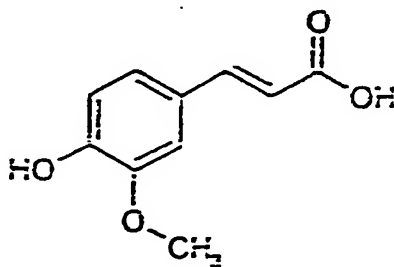
(CIX)

For the compounds (CV), (CVI), (CVII) and (CVIII) wherein a SH group is present, the corresponding compound  $SN(O)_s$ , wherein  $s$  is 1 or 2, can also be used instead of SH;

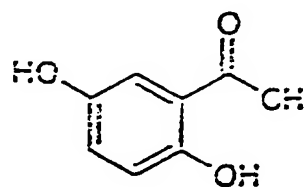
- hydroxyacids, selected from the following: gallic acid (formula DI), ferulic acid (DII), gentisic acid (DIII), citric acid (DIV), caffeic acid (DV), hydro caffeic acid (DVI), p-coumaric acid (DVII), vanillic acid (DVIII), chlorogenic acid (DIX), kynurenic acid (DX), syringic acid (DXI):



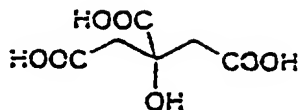
(DI)



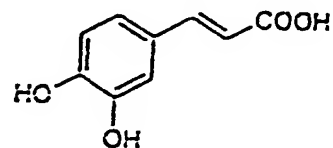
(DII)



(DIII)

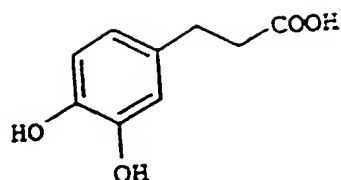


(DIV)

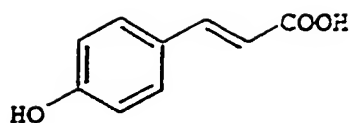


(DV)

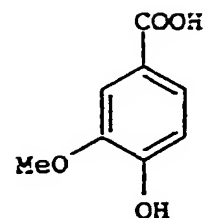




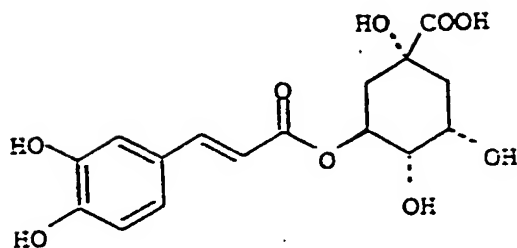
(DVI)



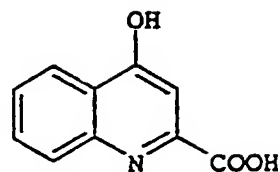
(DVII)



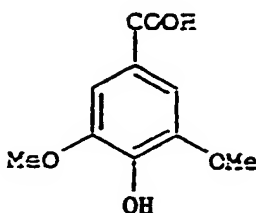
(DVIII)



(DIX)



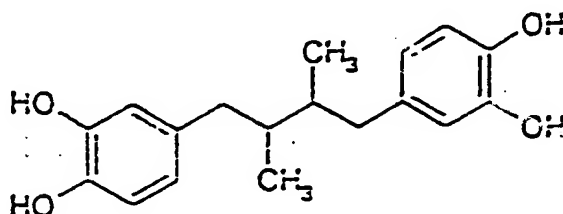
(DX)



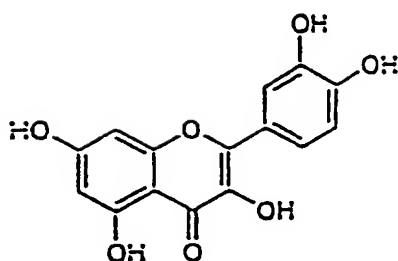
(DXI)

- Aromatic and heterocyclic mono- and polyalcohols, selected from the following: nordihydroguaiaretic acid (EI), quercetin (EII), catechin (EIII), kaempferol (EIV), sulphurethyne (EV), ascorbic acid (EVI), isoascorbic acid (EVII), hydroquinone (EVIII), gossypol (EIX), reductic acid (EX), methoxyhydroquinone (EXI), hydroxyhydroquinone (EXII), pro-

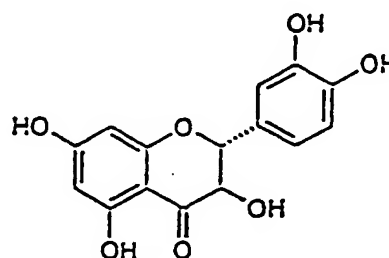
pyl gallate (EXIII), saccharose (EXIV), vitamin E (EXV), vitamin A (EXVI), 8-quinolol (EXVII), 3-tert-butyl-4-hydroxyanisole (EXVIII), 3-hydroxyflavone (EXIX), 3,5-tert-butyl-p-hydroxytoluene (EXX), p-tert-butyl phenol (EXXI), timolol (EXXII), xibornol (EXXIII), 3,5-di-tert-butyl-4-hydroxybenzyl-thioglycolate (EXXIV), 4'-hydroxybutyranilide (EXXV), guaiacol (EXXVI), tocol (EXXVII), isoeugenol (EXXVIII), eugenol (EXXIX), piperonyl alcohol (EXXX), allopurinol (EXXXI), conyferyl alcohol (EXXXII), 4-hydroxyphenethyl alcohol (EXXXIII), p-coumaric alcohol (EXXXIV), curcumin (EXXXV):



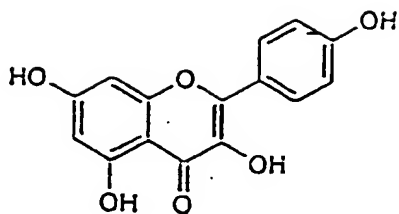
(EI)



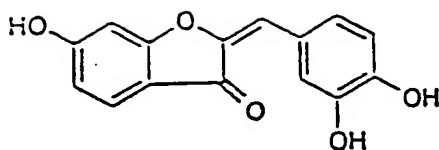
(EII)



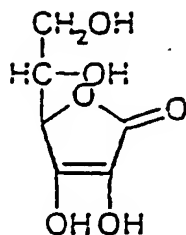
(EIII)



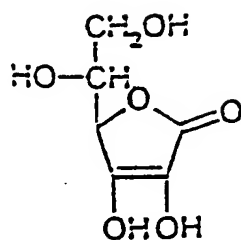
(EIV)



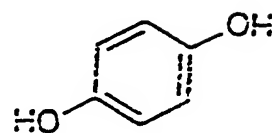
(EV)



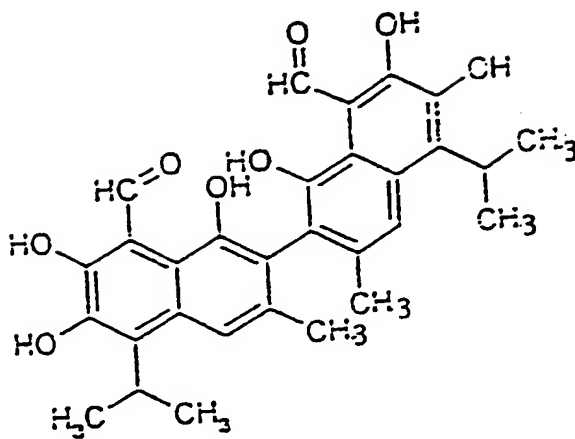
(EVI)



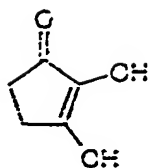
(EVII)



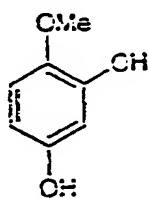
(EVIII)



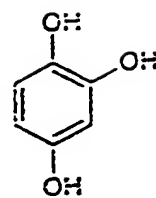
(EIX)



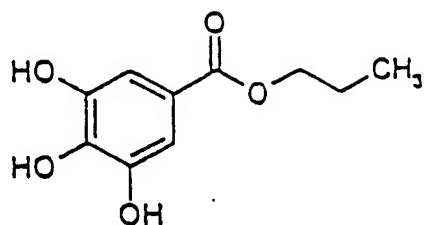
(EX)



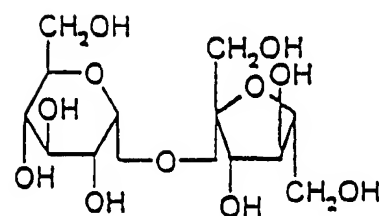
(EXI)



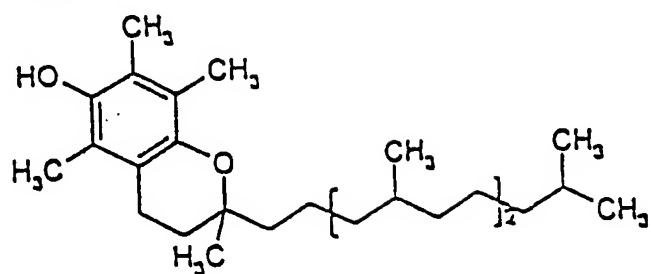
(EXII)



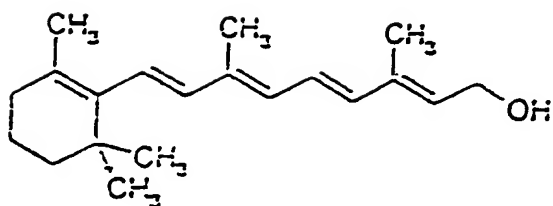
(EXIII)



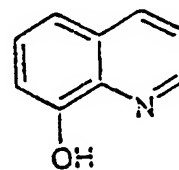
(EXIV)



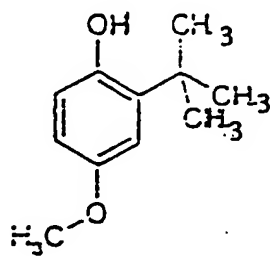
( EXV )



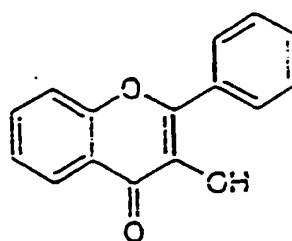
( EXVI )



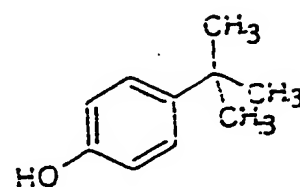
(EXVII)



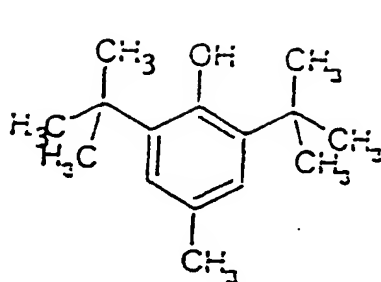
(EXVIII)



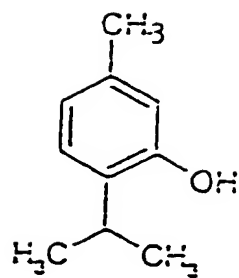
( EXIX )



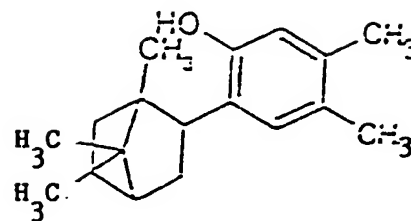
( EXXI )



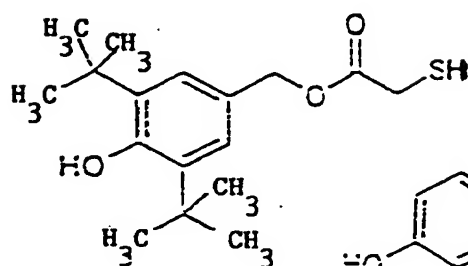
(EXX)



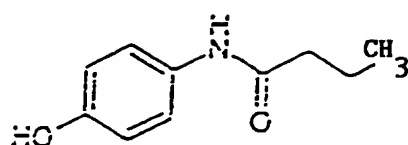
(EXXII)



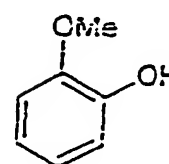
(EXXIII)



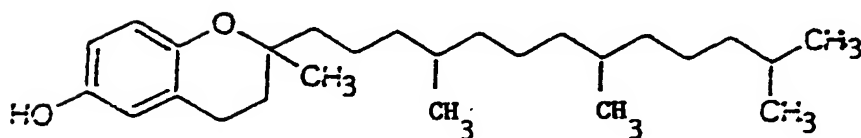
(EXXIV)



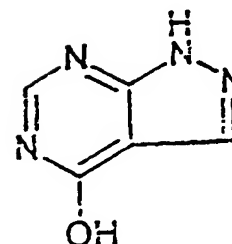
(EXXV)



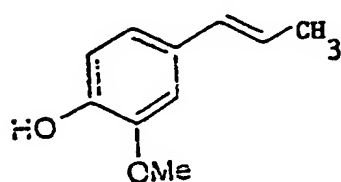
(EXXVI)



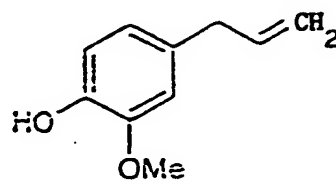
(EXXVII)



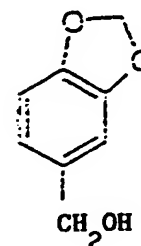
(EXXXI)



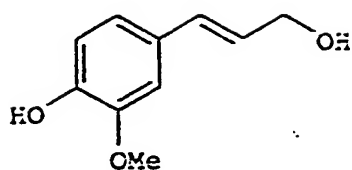
(EXXVIII)



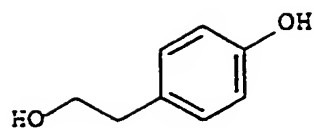
(EXXIX)



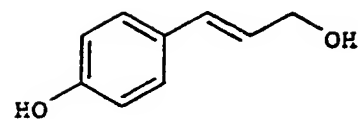
(EXXX)



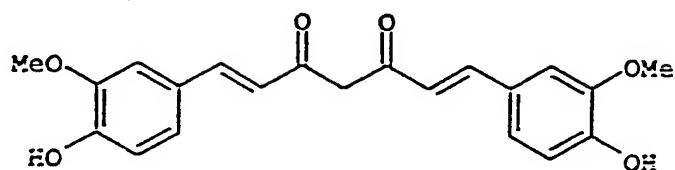
(EXXXII)



(EXXXIII)

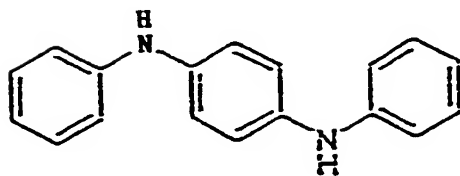


(EXXXIV)

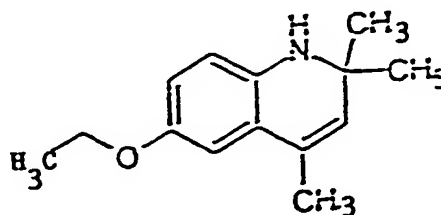


(EXXXV)

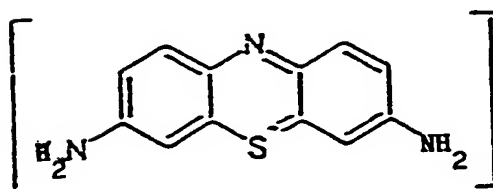
- aromatic and heterocyclic amines, selected from the following: N, N'-diphenyl-p-phenylenediamine (MI), ethoxyquin (MII), thionine (MIII), hydroxyurea (M-IV):



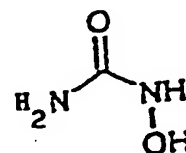
(MI)



(MII)

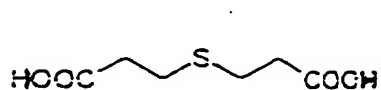


(MIII)

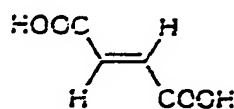


(MIV)

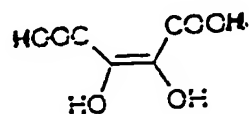
- Compounds containing at least a free acid function, selected from the following: 3,3'-thiodipropionic acid (NI), fumaric acid (NII), dihydroxymaleic acid (NIII), thiocctic acid (NIV), edetic acid (NV), bilirubin (NVI), 3,4-methylenedioxcinnamic acid (NVI-I), piperonylic acid (NVIII):



(NI)



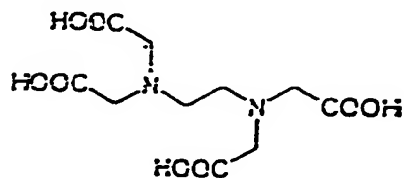
(NII)



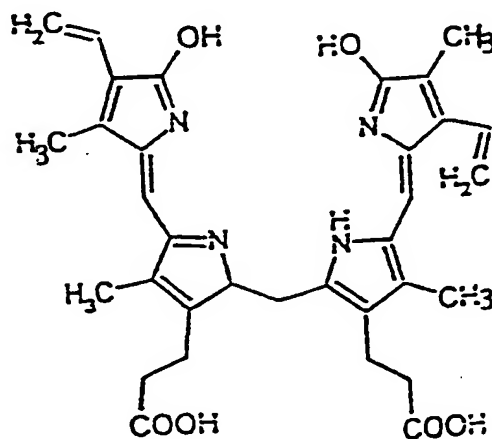
(NIII)



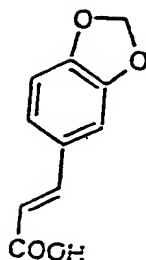
(NIV)



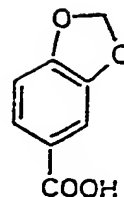
(NV)



(NVI)



(NVII)



(NVIII)

4. Compounds according to claims 2-3, wherein the precursor compounds of B are those meeting test 4.
5. Compounds according to claims 1-4 wherein B contains free reactive functions selected from one or more of the following groups: XZ and  $Z_I-N-Z_{II}$  wherein X, Z,  $Z_I$  and  $Z_{II}$  are as above defined, or COOH, =NH.
6. Compounds according to claim 5 wherein B is let react with the compounds of formula (III) having the free valence saturated with a reactive group such as to be capable to react with the free reactive function of B:



wherein:

$n_{IX}$  is an integer between 0 and 3, preferably 1;

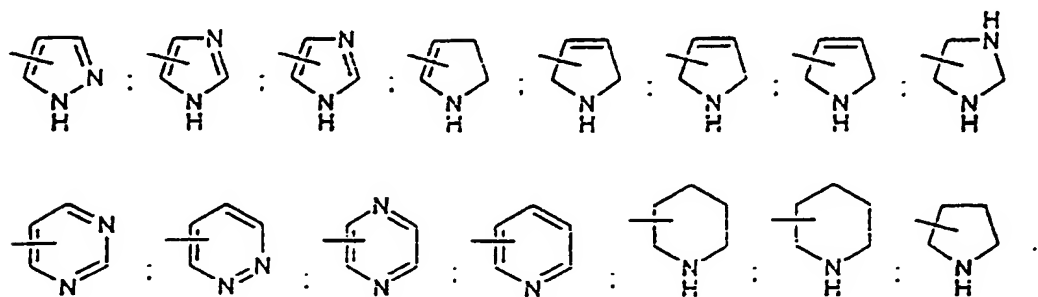
$R_{TIX}$ ,  $R_{TIX'}$ , equal to or different from each other are H or a linear or branched  $C_1$ - $C_4$  alkyl; preferably  $R_{TIX}$ ,  $R_{TIX'}$ , are H.



$Y^3$  is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen atom, said ring having 5 or 6 atoms.

7. Compounds according to claim 6 wherein

$Y^3$  in formula (III) is selected from the following:



8. Compounds according to claim 7 wherein  $Y^3$  is  $Y^{12}$  (pyridyl).
9. Compounds according to claims 1-8, wherein the precursor drugs of the formula (I) compounds are selected from the following: anti-inflammatory, analgesic drugs, bronchodilators and drugs active on the cholinergic system, expectorant-mucolytic drugs, antiasthmatic-antiallergic, antihistaminic drugs, ACE-inhibitors, beta-blockers, antithrombotic drugs, vasodilators, antidiabetic, antitumoral, antiulcer, antihyperlipidemic, antibiotic, antiviral drugs, bone reabsorption inhibitors, antidementia drugs.
10. Compounds according to claim 9, wherein the precursor drugs are selected from the following:

anti-inflammatory drugs: aceclofenac, acemetacin, acetyl-salicylic acid, 5-aminoacetylsalicylic acid, alclofenac, alminoprofen, amfenac, bendazac, bermoprofen,  $\alpha$ -bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen, cinmetacin, clidanac, clopirac, sodium diclofenac, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, olsalazine, oxaceprol, oxaprozin, oxyphenbutazone, parsalimide, perisoxal, phenyl acetylsalicylate, pyrazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicilamide O-acetic acid, salicylsulphuric acid, salsalate, sulindac, suprofen, suxibuzone, tenoxicam, tiaprofenic acid, tiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepirac, tomoxiprol;

analgesic drugs: acetaminophen, acetaminosalol, aminochlorthenoxazin, acetylsalicylic 2-amino-4-picoline acid, acetylsalicylsalicylic acid, anileridine, benoxaprofen benzylmorphine, 5-bromosalicylic acetate

acid, buccetin, buprenorphine, butorphanol, capsaicine, cinchophen, ciramadol, clometacin, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimepheptanol, dipyroacetyl, eptazocine, ethoxazene, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, p-lactophenetide, levorphanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nicomorphine, norlevorphanol, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, phenocoll, phenoperidine, phenylbutazone, phenylsalicylate, phenylramidol, salicin, salicylamide, tiorphan, tramadol, diacerein, actarit;

bronchodilators and drugs active on the cholinergic system: acefylline, albuterol, bambuterol, bamifylline, bevonium methyl sulphate, bitolterol, carbuterol, clenbuterol, chlorprenaline, dioxethedrine, diphylline, ephedrine, epinephrine, eprozinol, etafredine, ethyl norepinephrine, etofylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetharine, isoprotenerol, mabuterol, metaproterenol, oxybutinyn, oxitropium bromide, pirbuterol, procaterol, protokylol, proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-teobromineacetic acid, tiotropium bromide, tretoquinol, tulobuterol, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-

tetrahydro-pyridin-4-ylmethyl)acetamide ;

expectorant/mucolytic drugs: ambroxol, bromhexine, domiodol, erdosteine, guaiacol, guaifenesin, iodinated glycerol, letosteine, mesna, sobrerol, stepronin, terpin, tiopronin;

antiasmatic/antiallergic antihistaminic drugs: acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, histamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron s, montelukast, nedocromil, repirinast, seratrodist, suplatast tosylate, terfenadine, tiaramide, urushiol, bromhexine;

ACE-inhibitors: alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, losartan, moveltipril, naphthopidil, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, urapidil;

beta-blockers: acebutolol, alprenolol, amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol,

sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;

antithrombotic and vasoactive drugs: acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betahistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, dalteparin, dipyridamole, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, heparin, lamifiban, midodrine, nadroparin, nicotiny alcohol, nylidrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, paveroline, reviparin sodium salt, ridogrel, suloctidil, tinofedrine, tinzaparin, triflusal, xanthinol niacinatete;

antidiabetic drugs: acarbose, carbutamide, glibornuride glybuthiazol(e), miglitol, repaglinide, troglitazone, 1-butyl-3-metanyl-urea, tolrestat, nicotinamide;

antitumoral drugs: ancitabine, anthramycin, azacitidine, azaserine, 6-azauridine, bicalutamide, carubicin, carzinophilin, chlorambucil, chlorozotocin, cytarabine, daunorubicin, defosfamide, demecolcine, denopterin, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicin, droloxifene, edatrexate, eflornithine, enocitabine, epirubicin, epitiostanol,

etanidazole, etoposide, fenretinide, fludarabine, fluorouracil, gemcitabine, hexestrol, idarubicin, lonidamine, mannomustine, melphalan, menogaril, 6-mercaptopurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, mycophenolic acid, ninopterin, nogalamycin, paclitaxel, pentostatin, pirarubicin, piritrexim, plicamycin, podophyllic acid, porfimer sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, thiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicin;

antiulcer drugs:  $\epsilon$ -acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecabet, enprostil, esaprazole, irsogladine, misoprostol, omeprazole, ornoprostil, pantoprazole, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil;

anti-hyperlipidemic drugs: atorvastatin, cilastatin, dermostatin, fluvastatin, lovastatin, mevastatin, nystatin, pentostatin, pepstatin, sodium pravastatin, simvastatin;

antibiotics: amdinocillin, amoxicillin, ampicillin, apalcillin, apicycline, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl pe-

nicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephradine sodium, cephalixin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephalixin sodium, cephradine, chloramphenicol, chlortetracycline, cinoxacin, clavulanic acid, clometocillin, cloxacillin, cyclacillin, cycloserine, demeclocycline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacillin, hetacillin, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, meclocycline, meropenem, metampicillin, methacycline, methicillin sodium, mezlocillin, minocycline, moxalactam, mupirocin, myxin, negamycin, novobiocin, oxacillin, pamipenem, penicillin G potassium salt, penicillin N, penicillin O, penicillin V, phenethicillin potassium salt, pipacycline, piperacillin, pirlimycin, porfiromycin, propycillin, quinacillin, ritipenem, rolitetracycline, sancycline,

sedecamycin, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidin, azithromycin, clarithromycin, dirithromycin, enviomycin, erythromycin, josamycin, midecamycin, miokamycin, oleandomycin, rifabutin, rifamide, rifamycin, rifaximin, rokitamycin, spiramycin, troleandomycin, viomycin, virginiamycin;

amikacin, apramycin, arbekacin, dibekacin, dihydrostreptomycin, fortimicins, gentamicin, micronomicin, neomycin, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin; bacampicillin, cefcapene pivoxil, cefpodoxime proxetil, panipenem, pivampicillin, pivcefalexin, sultamicillin, talampicillin;

carbomycin, clindamycin, lincomycin, mikamycin, rosaramicin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, flumequine, grepafloxacin, lomefloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rufloxacin, sparfloxacin, tosufloxacin, trovafloxacin, clomocycline, guamecycline, oxytetracycline, nifurpirinol, nifurprazine;

p-aminosalicylic acid, p-aminosalicylic acid hydrazide, clofazimine, deoxydihydrostreptomycin, ethambutol, glyconiazide, isoniazid, opiniazide, phenyl



aminosalicylate, rifampin, rifapentine, salinazid, 4-4'-sulfynyldianiline, acediasulfone, dapsone, succisulfone, p-sulfanilylbenzyl amine, thiazolsulfone, acetyl sulfamethoxypyrazine, mafenide, 4'-(methylsulfamoyl)sulfanilanilide, salazosulfadimidine, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 2-p-sulfanilylanilinoethanol, N<sup>4</sup>-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfisomidine, sulfisoxazole, 4-sulfanilamido salicylic acid; negamycin, carumonan, cloxyquin, nitroxoline, arginine, metronidazole;

antiviral drugs: aciclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxin, ribavirin, rimantadine, saquinavir,

sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;

bone resorption inhibitors: alendronic acid, butedronic acid, etidronic acid, oxydronic acid, pamidronic acid, risedronic acid;

antidementia drugs: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

11. Compounds according to claims 9-10, wherein the precursor drugs are selected from the following:

anti-inflammatory drugs: acetylsalicylic acid, 5-aminoacetylsalicylic acid, carprofen, diclofenac sodium, diflunisal, etodolac, flufenamic acid, flunixin, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, naproxen, niflumic acid, olsalazine, piroxicam, salsalate, sulindac, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, tolmetin, zomepirac, tomoxiprol;

analgesic drugs: acetaminophen, acetylsalicylsalicylic acid, benoxaprofen, buprenorphine, butorphanol, capsaicin, diacerein, dihydrocodeine, ethylmorphine, eugenol, phenylbutazone, meptazinol, morphine, nalbuphine, pentazocine, thiorphan, tramadol, actarit;

bronchodilators and drugs active on the cholinergic

system: albuterol, carbuterol, clenbuterol, difhylline, etofylline, fenoterol, ipratropium bromide, metaproterenol, oxybutynin, pirbuterol, salmeterol, terbutaline, tiotropium bromide, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetrahydro-pyridin-4-ylmethyl) acetamide;

expectorant/mucolytic drugs: ambroxol, bromexine, guaia-col, sobrerol;

antiasthmatic/antiallergic antihistaminic drugs:

cetirizine, chromoglycate, histamine, levocabastine, lodoxamide, montelukast, terfenadine, bromexine;

ACE-inhibitors: captopril, enalapril, lisinopril, losartan, ramipril;

beta blockers: alprenolol, atenolol, bupranolol, labetalol, metipranolol, metoprolol, pindolol, propranolol, timolol;

antithrombotic and vasoactive drugs: acetylsalicylic acid, acetorphan, argatroban, clopidogrel, dalteparin, dipyridamole, enoxaparin, heparin, iloprost, midodrine, ozagrel, phenylpropanolamine, trifusal;

antidiabetic drugs: tolrestat, nicotinamide;

antitumoral drugs: anthramycin, daunorubicin, doxorubicin, epirubicin, fluorouracyl, methotrexate, vinblastine;

antiulcer drugs: cimetidine, omeprazole, pantoprazole;

antihyperlipidemic drugs: lovastatin, pravastatin sodium,

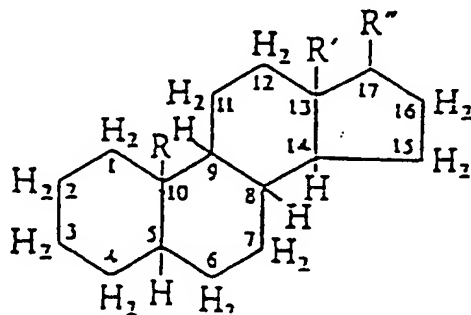
simvastatin;

antibiotics: amoxicillin, ampicillin, aztreonam, biapenem, carbenecillin, cefaclor, cefadroxil, cefamandole, cefatrizine, cefoxitin, clavulanic acid, dicloxacillin, imipenem, meclocycline, methacycline, moxalactam, panipenem, sulbactam, azithromycin, erythromycin, josamycin, miokamycin, rifabutine, rifamide, rifamycin, gentamicin, paromomycin, sisomicin, bacampicillin, carbomycin, clindamycin, ciprofloxacin, clinafloxacin, difloxacin, enrofloxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pipemidic acid, apicycline, clomocycline, oxytetracycline, nifurpirinol, nifurprazine, isoniazid, rifampin, rifapentine, dapsone, thiazolsulfone, sulfamethoxazole, sulfamoxole, metronidazole, arginine;

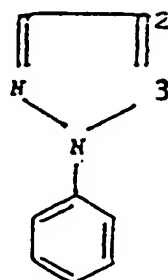
antiviral drugs: acyclovir, famciclovir, ganciclovir, penciclovir, ribavirin, vidarabine, zidovudine;

bone resorption inhibitors: alendronic acid, etidronic acid, pamidronic acid.

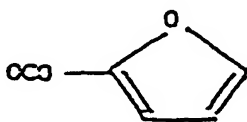
12. Compounds according to claims 1-8 wherein the precursor drugs are steroidal compounds wherein A = R-, having the following structure:



wherein in substitution of the hydrogens of the CH groups or of the two hydrogens of the CH<sub>2</sub> groups mentioned in the general formula, there may be the following substituents;  
 in position 1-2: there may be a double bond;;  
 in position 2-3: there may be the following substituent:

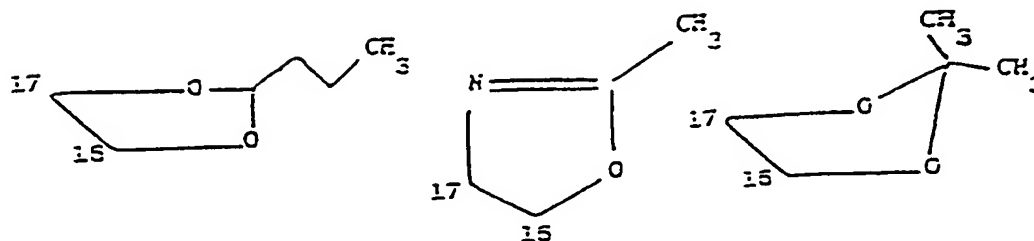


in position 2: there may be Cl, Br;  
 in position 3: there may be CO, -O-CH<sub>2</sub>-CH<sub>2</sub>-Cl, OH;  
 in position 3-4: there may be a double bond;  
 in position 4-5: there may be a double bond;  
 in position 5-6: there may be a double bond;  
 in position 5-10: there may be a double bond;  
 in position 6: there may be Cl, F, CH<sub>3</sub>, -CHO;  
 in position 7: there may be Cl, OH;  
 in position 9: there may be Cl, F;  
 in position 11: there may be OH, CO, Cl, CH<sub>3</sub>;  
 in position 16: there may be CH<sub>3</sub>, OH, =CH<sub>2</sub>;  
 in position 17: there may be OH, CH<sub>3</sub>, OCO(O)<sub>ua</sub>(CH<sub>2</sub>)<sub>va</sub>CH<sub>3</sub>,  
 C≡CH or



wherein  $u_a$  is an integer equal to 0 or 1,  $v_a$  is an integer from 0 to 4;

in position 16-17: there may be the following groups:

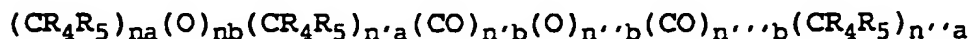


$R$  and  $R'$ , equal to or different from each other, can be hydrogen or linear or branched alkyls from 1 to 4 carbon atoms, preferably  $R = R' = CH_3$ ;

$R''$  is  $-(CO-L)_t-(L)_{t_2}-(X_O^I)_{t_1}-$

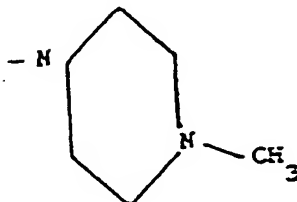
wherein  $t$ ,  $t_1$  and  $t_2$  are integers equal to or different from each other equal to 0 or 1, with the proviso that when  $t = 0$   $t_2 = 1$  and when  $t = 1$   $t_2 = 0$ , and that  $t$  and  $t_1$ , or  $t_2$  and  $t_1$ , cannot contemporaneously be equal to 0 when  $A$  does not contain  $-OH$  groups;

the bivalent bridging group  $L$  is selected from:



wherein  $n_a$ ,  $n'a$ , and  $n''a$ , equal to or different from each other, are integers from 0 to 6, preferably 1-3;  $n_b$ ,  $n'b$ ,  $n''b$  and  $n''''b$ , equal to or different from each other, are integers equal to 0 or 1;  $R_4$ ,  $R_5$ , equal to or different from each other, are selected from H, linear or branched alkyl from 1 to 5 carbon atoms, preferably from 1 to 3;

$X_0^I$  is X as above defined, or equal to  $X_2^I$  wherein  $X_2^I$  is equal to OH, CH<sub>3</sub>, Cl, N(-CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>, SCH<sub>2</sub>F, SH, or



13. Compounds according to claim 12 wherein R" = -CO-CH<sub>2</sub>OH, -CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>-COOH.
14. Compounds according to claims 12-13 wherein the precursor steroids are selected from those having the hydroxyl function in position 3 and/or in position 11, and/or having in R" an hydroxyl or carboxylic function in terminal position.
15. Compounds according to claims 12-14 wherein the precursor steroids are selected from the following: Budesonide, Hydrocortisone, Alclomethasone, Algestone, Beclomethasone, Betamethasone, Chloroprednisone, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Cortisone, Corticosterone, Deflazacort, Desonide, Desoximethasone, Dexamethasone, Diflorasone Diflucortolone, Difluprednate, Fluzacort, Flucloronide, Flumethasone, Flunisolide, Fluocinolone Acetonide, Fluocinonide, Fluocortyn Butyl, Fluocortolone, Fluorometholone, Fluperolone Acetate, Fluprednidene Acetate, Fluprednisolone, Flurandrenolide, Formocortal, Halcinonide, Halobetasol Propionate, Halomethasone, Halopredone Acetate, Hydrocortamate,

Loteprednol Etabonate, Medrysone, Meprednisone, Methylprednisolone, Momethasone Furoate, Paramethasone, Prednicarbate, Prednisolone, Prednisolone 25-Diethylaminoacetate, Prednisolone Sodium Phosphate, Prednisone, Prednival, Prednylidene, Rimexolone, Triamcinolone, Triamcinolone Acetonide, 21-Acetoxyprogesterone, Cortivazol, Amcinonide, Fluticasone Propionate, Mazipredone, Tixocortol, Triamcinolone Hexacetonide, Ursodesoxycholic acid, Chenodeoxycholic acid, Mitatrienediol, Moxestrol, Ethynylestradiol, Estradiol, Mestranol.

16. Compounds or salts, or their compositions according to claims 1-15 for use as a medicament.
17. Use of the compounds or salts, or their compositions according to claims 1-15 for the preparation of drugs for the therapeutic oxidative stress application.
18. Pharmaceutical formulations containing as active principle the compounds or their salts of claims 1-15.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
19 October 2000 (19.10.2000)

PCT

(10) International Publication Number  
WO 00/61549 A3

(51) International Patent Classification<sup>7</sup>: C07C 327/34, 69/618, 69/65, C07D 207/16, C07C 211/49, 219/10, C07D 209/28, 233/64, 277/06, 277/14, 295/088, 309/30, 401/12, 407/04, 417/12, 473/08, 495/04, 499/32, C07F 9/38, C07H 15/252, A61K 31/16

(74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni 2, I-20129 Milano (IT).

(21) International Application Number: PCT/EP00/03237

(81) Designated States (*national*): AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA.

(22) International Filing Date: 11 April 2000 (11.04.2000)

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
MI99A000750 13 April 1999 (13.04.1999) IT

Published:  
— with international search report

(71) Applicant (*for all designated States except US*): NICOX S.A. [FR/FR]; 45, Avenue Kléber, F-75116 Paris (FR).

(88) Date of publication of the international search report:  
3 January 2002

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT).

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 00/61549 A3

(54) Title: PHARMACEUTICAL COMPOUNDS

(57) Abstract: Compounds or their salts of general formula (I): A-(B) wherein A = R-T<sub>1</sub>-, wherein R is the drug radical and T<sub>1</sub> = (CO)<sub>t</sub> or (X)<sub>t</sub>, wherein X = O, S, NR<sub>1C</sub>, R<sub>1C</sub> is H or an alkyl having from 1 to 5 carbon atoms, or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1; B = -T<sub>B</sub>-X<sub>2</sub> wherein T<sub>B</sub> = (CO) when t = 0, T<sub>B</sub> = X when t' = -, X being as above defined; X<sub>2</sub>, monovalent radical, is such that the precursor drug of A and the precursor of B respectively meet the pharmacological tests described in the application.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 00/03237

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C327/34 C07C69/618 C07C69/65 C07D207/16 C07C211/49  
C07C219/10 C07D209/28 C07D233/64 C07D277/06 C07D277/14  
C07D295/088 C07D309/30 C07D401/12 C07D407/04 C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 052 910 A (ALBERTO REINER & C.) 2 June 1982 (1982-06-02)  the whole document	1,3, 9-11, 16-18
X	EP 0 255 164 A (ZAMBON) 3 February 1988 (1988-02-03)  the whole document	1,3, 9-11,16, 18
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*G\* document member of the same patent family

Date of the actual completion of the international search

9 April 2001

Date of mailing of the international search report

08/05/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

English, R

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/03237

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D473/08 C07D495/04 C07D499/32 C07F9/38 C07H15/252  
A61K31/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 107, no. 7, 17 August 1987 (1987-08-17) Columbus, Ohio, US; abstract no. 59488w, page 781; XP002164473 abstract - & ES 8 609 231 A (FARMHISPANIA) 16 December 1986 (1986-12-16) ---	1,3, 9-11, 16-18
X	EP 0 103 320 A (EDMOND PHARMA) 21 March 1984 (1984-03-21)  example 3 ---	1,3, 9-11,16, 18
A	WO 98 47534 A (KLINGE PHARMA) 29 October 1998 (1998-10-29) page 12 -page 13 -----	16-18



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance  
 \*E\* earlier document but published on or after the International filing date  
 \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 \*O\* document referring to an oral disclosure, use, exhibition or other means  
 \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
 \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
 \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  
 \*&\* document member of the same patent family

Date of the actual completion of the international search

9 April 2001

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax (+31-70) 340-3016

Authorized officer

English, R

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Claims Nos.: 1-11,15-18 (not searched in part), 12-15 (not searched)

Present claims 1-18 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Furthermore, present claims 1-18 relate to compounds defined by reference to a desirable characteristic or property, namely that their precursors attain a certain level of anti-oxidative activity evidenced according to test 4 and test 5 (which are elucidated in claim 1) and at least a certain level of at least one of (a) gastrointestinal damage, (b) apoptosis or (c) hepatic damage and/or gastric damage and/or cardiovascular damage evidenced according to tests 1 to 3 (also elucidated in claim 1). Since the combination these properties (anti-oxidative activity and lower toxicity) is in fact the problem to be solved by the compounds of the present application (see page 9, lines 1-11 of the description), this means that the claimed compounds are defined in terms of their being a solution to this problem.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds prepared in examples 1-28.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Publication No  
PCT/EP 00/03237

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0052910 A	02-06-1982	IT 1134458 B	13-08-1986
		CH 648297 A	15-03-1985
		DE 3169890 D	15-05-1985
		JP 1028744 B	05-06-1989
		JP 1543778 C	15-02-1990
		JP 57167963 A	16-10-1982
EP 0255164 A	03-02-1988	IT 1213301 B	20-12-1989
		AT 96150 T	15-11-1993
		AT 179071 T	15-05-1999
		DE 3752272 D	27-05-1999
		DE 3752272 T	30-12-1999
		DE 3787844 D	25-11-1993
		DE 3787844 T	10-02-1994
		EP 0565146 A	13-10-1993
		ES 2060592 T	01-12-1994
		ES 2133351 T	16-09-1999
		GR 3030822 T	30-11-1999
		JP 63023857 A	01-02-1988
		US 4806567 A	21-02-1989
		US 4812477 A	14-03-1989
ES 8609231 A	16-12-1986	ES 549540 D	01-09-1986
EP 0103320 A	21-03-1984	IT 1190987 B	24-02-1988
		AT 27270 T	15-06-1987
		BE 897617 A	16-12-1983
		CA 1202317 A	25-03-1986
		DE 3371627 D	25-06-1987
		FR 2532647 A	09-03-1984
		US 4563443 A	07-01-1986
WO 9847534 A	29-10-1998	AU 2387997 A	13-11-1998
		EP 0971743 A	19-01-2000

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.